International Research Center
on Cannabis and Mental Health

From:
International Research Center on Cannabis and Mental Health
1115 Broadway, 11th floor
New York, NY 10010
(917) 565-9046

To:
Division of Dockets Management (HF A-305) Food and Drug Administration
5630 Fishers Lane, Room I030
Rockville, MD 20852

Re: Dietary Supplement Products Containing Cannabis or Cannabis Derived Compounds
Docket FDA-2019-N-1482

Dear Madam/Sir,

My name is Jahan Marcu, Ph.D, Chief Science Officer at the *International Research Center on Cannabis and Mental Health* (IRCCMH). My colleague and IRCCMH Co-founder and CEO, Dr. Jan Roberts, LCSW, and I concur with the FDA's consistent focus on protecting the public health. We believe our respective backgrounds can be helpful to the FDA's deliberations on Cannabis and Hemp-Derived Compounds. We are accordingly submitting this comment for consideration (in regard to the FDA's Working Group on Cannabis Containing Products) and would be pleased to be a resource (as deemed appropriate) for the FDA in its deliberations around this important topic. If useful, this could include collaboration on the topic broadly as well as providing data from IRCCMH safety studies; or conducting additional safety studies if needed.

In order to provide useful context, the International Research Center on Cannabis and Mental Health is a community-based research institute based in New York City. IRCCMH was founded with a center grant from New York University where Dr. Roberts. IRCCMH leverages a strong industry network, collaborating with universities, researchers, foundations, state institutions, and others to leverage the highest caliber talent in the field.

In addition to being a Co-Founder of IRCCMH, I have over 15 years of experience in the cannabis industry, stemming back to when I initially volunteered for Americans for Safe Access and was Director of their Patient Focused Certification program (an organization and program that also emphasized public health and safety). I am also fortunate to have earned a Ph.D. focused on the endocannabinoid system (with research on the structure and function of cannabinoid receptors, molecular pharmacology of the endocannabinoid system, and the role of the ECS in bone). That education was extremely instructive about the potential medical benefits worthy of significant research (and support). My professional roles have included the CSO role at Americans for Safe Access, as well as chairmanships at the Cannabis Chemistry Sub-division

of the American Chemical Society, American Herbal Products Association, ASTM D37 Cannabis Committee, and have served on other expert government advisory, trade association committees, and scientific organizations. I am currently an advisor to the State of Delaware's Medical Marijuana Program.

Attached to this letter are resources, research articles, and white papers we have authored or contributed to. This includes topics ranging from cannabinoid receptor pharmacology, drug development, CBD & THC cancer research, mental health research, and a guidance document that maybe particularly useful for your current deliberations (an FDA style 8-factor analysis of cannabis).

Jan Roberts, LCSW, DSW provides IRCCMH with invaluable insights when it comes to direct clinical experience with patients. She owns and operates one of the largest collaborative care practices in the mid-Atlantic region, *Partners in Health and Wellbeing.* She is also one of the founders for the first integrative care center in Delaware, Integrative Health Delaware – A Center for Health & Research. Additionally, Dr. Roberts teaches at NYU Silver School of Social Work and is also working on a study of Mental Health Clinicians' and Knowledge & Attitudes on Cannabis. Dr. Roberts was guest-editor for a special issue on Cannabis and Mental Health for the Clinical Social Work Journal. Her decision to create IRCCMH stemmed from her dedication to provide patients with the latest objective research at the therapeutic use of cannabis in mood regulation and the treatment of other mental health conditions. Dr. Roberts' focus is on the clinical application of cannabis in mental health settings and focusing on maladaptive coping strategies rather than a substance-based approach to treating addictions. She is dedicated to educating fellow mental health clinicians on current research findings to ensure more physicians and other healthcare providers are knowledgeable about cannabis, the endocannabinoid system and the impact on mental health outcomes. In addition to her research and education endeavors, Dr. Roberts continues to treat patients. This has resulted in her firsthand knowledge of the patient safety and concern issues related to CBD products. As a result, she keenly believes that research should influence policy and not vice-versa – an important driver for IRCCMH to help contribute to informed policy decisions. Dr. Roberts is also on Governor's appointee to the State of Delaware's Medical Marijuana Advisory committee.

The IRCCMH and I have conducted small studies aimed at assisting policymakers to make the most informed decisions. We have also advised states adopting or revising cannabis regulations. Additionally, our prior experience includes contributions to the first national standards (adopted by 19 States) for the cannabis industry with the American Herbal Products Association's Cannabis Committee. I was also a core contributor of the *American Herbal Pharmacopoeia Cannabis Monograph* and co-author of a CBD Labeling study published in *JAMA*; this study demonstrated inaccurate labeling among the majority of tested products. Insights gained from work in these areas demonstrate the many areas warranting substantial medical research. It has also highlighted the need for clear regulations, consistent industry standards, and oversight driven by an emphasis on the public health.

We urge the FDA to consider simple guidelines for hemp products, and to encourage more funding and legitimate pathways to study products that are commercially available, in the NIH or USDA budgets to fully understand and appreciate the use of cannabinoids in health and disease.

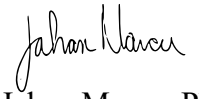
We appreciate that the FDA is expediting its work to address the many questions about CBD. This is a vital national issue that directly impacts the public health. While public health must always be the driver, decisions surrounding regulations on CBD also affect multiple agencies and constituents. In the case of CBD, regulations that are holistic in their approach can certainly accomplish the FDA's goal to protect the public health.

We concur with many submitted comments provided by the public and suggest the inclusion of core guidelines in the FDA's deliberations. These could include:

1. A pathway and guidance documents should be created for basic clinical study for any Hemp-CBD or CBD product being distributed to be on the market.
2. Education and trainings need to be available through accredited or approved organizations to help inform doctors, law enforcement, and all sectors of the cannabis and hemp industry. ISO accreditation for certifying bodies would be a simple requirement for organizations providing education or training services regarding hemp and CBD.
3. All other botanical additives should be GRAS per FDA or have safety data to support the use or inclusion in formulation
4. The product should be tested for quality, potency, and shelf-life stability according to existing standards; incorporating existing standards such as pharmacopoeias and industry consensus standards
5. The product should be tested for pesticides, heavy metals, and contaminants at laboratory with accredited methods.

Thank you for the opportunity to offer our submission on this critical topic. Timely, informed and appropriate regulations can serve the public interest while requiring reasonable industry regulations to be followed. If we can be of assistance in efforts to protect the public health when it comes to cannabis, please do not hesitate to contact us as appropriate.

Respectfully,



Jahan Marcu, Ph.D.
Chief Science Officer
International Research Center on
Cannabis and Mental Health
1115 Broadway, 11th Floor
New York, NY 10010
Office: 917-565-9046

Selected Resources and Bibliography

1. Marcu, J. P. & Phifer, R. Alternatives to Address Cannabis Intoxication in the Workplace and Clinical Trials. *The 256th American Chemical Society National Meeting Exposition* (2018).

2. Russo, E. B. & Marcu, J. Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads. *Adv Pharmacol* **80,** 67–134 (2017). (Attached)

3. Bonn-Miller, M. O. *et al.* Labeling Accuracy of Cannabidiol Extracts Sold Online. *Jama* **318,** 1708–1709 (2017). (Attached)

4. Marcu, J. P. An Overview of Major and Minor Phytocannabinoids. *Neuropathology of Drug Addiction and Substance Misuse* 672 678 (2016). doi:10.1016/b978-0-12-800213-1.00062-6

5. Marcu, J. P. Scheduling Cannabis: A Preparatory Document For FDA'S 8 Factor Analysis On Cannabis. (2016). (Attached)

6. Shore, D. *et al.* Allosteric modulation of a cannabinoid G protein-coupled receptor: binding site elucidation and relationship to G protein signaling. *J Biol Chem* **289,** 5828 5845 (2014).

7. Marcu, J. *et al.* Novel Insights into CB1 Cannabinoid Receptor Signaling: A Key Interaction Identified between the Extracellular-3 Loop and Transmembrane Helix 2. *J Pharmacol Exp Ther* **345,** 189–197 (2013).

8. Marcu, J. P. *et al.* Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Mol Cancer Ther* **9,** 180 189 (2010).

9. Marcu, J., Console-Bram, L. & Abood, M. E. Current Cannabinoid Receptor Nomenclature and Pharmacological Principles. *Endocannabinoid Regulation of Monoamines in Psychiatric and Neurological Disorders* 25 54 (2013). doi:10.1007/978-1-4614-7940-6_3

10. Marcu, J. P. & Schechter, J. B. Chapter 66 - Molecular Pharmacology of CB1 and CB2 Cannabinoid Receptors. *Part IV Cannabinoids Sect Molecular Cell Aspects* 1 9 (2015). doi:10.1016/b978-0-12-800213-1.00066-3

11. Roberts, J. Medical Cannabis in Adult Mental Health Settings: Reconstructing One of the Most Maligned Medications in the United States. *Clin Soc Work J* **40,** 1 9 (2018). (Attached)

12. Marcu, J. (2015) How Safe is Your Vape Pen? Project CBD science advisor Jahan Marcu, PhD, reports on the hidden dangers of propylene glycol and vape pens that smolder. www.projectcbd.org/industry/how-safe-your-vape-pen

Publications and Resources (Following Page)

Letters

RESEARCH LETTER

Labeling Accuracy of Cannabidiol Extracts Sold Online

There is growing consumer demand for cannabidiol (CBD), a constituent of the cannabis plant, due to its purported medicinal benefits for myriad health conditions.[1] Viscous plant-derived extracts, suspended in oil, alcohol (tincture), or vaporization liquid, represent most of the retail market for CBD. Discrepancies between federal and state cannabis laws have resulted in inadequate regulation and oversight, leading to inaccurate labeling of some products.[2] To maximize sampling and ensure representativeness of available products, we examined the label accuracy of CBD products sold online, including identification of present but unlabeled cannabinoids.

Methods | Internet searches (keywords: *CBD*, *cannabidiol*, *oil*, *tincture*, *vape*) were performed between September 12, 2016, and October 15, 2016, to identify CBD products available for online retail purchase that included CBD content on packaging. Products with identical formulation as another product under the same brand were excluded. All unique CBD extracts that met these criteria were purchased. Products were stored according to packaging instructions, or if none were provided, in a cool, dry space. Within 2 weeks of receipt, product labels were replaced with blinded study identifiers and sent to the laboratories at Botanacor Services for analysis of cannabinoid content (cannabidiol, cannabidiolic acid, cannabigerol, cannabinol, Δ-9-tetrahydrocannabinol, Δ-9-tetrahydrocannabibolic acid [THC]) using high-performance liquid chromatography (in triplicate; lower limit of quantification, ≤0.3170% wt/wt). A 10-point method validation procedure was used to determine the appropriate sample preparation and analytical method. Triplicate test results were averaged and reported by product weight. Data were analyzed using SPSS Statistics (IBM), version 23, with descriptive analyses and a 2-tailed χ^2 (α <.05). Consistent with other herbal products in the US Pharmacopeia and emerging standards from medicinal cannabis industry leaders, a ±10% allowable variance was used for product labeling (ie, accurately labeled = 90%-110% labeled value, underlabeled >110% labeled value, and overlabeled <90% labeled value).

Results | Eighty-four products were purchased and analyzed (from 31 companies). Observed CBD concentration ranged between 0.10 mg/mL and 655.27 mg/mL (median, 9.45 mg/mL). Median labeled concentration was 15.00 mg/mL (range, 1.33-800.00). With respect to CBD, 42.85% (95% CI, 32.82%-53.53%) of products were underlabeled (n = 36), 26.19% (95% CI, 17.98%-36.48%) were overlabeled (n = 22), and 30.95% (95% CI, 22.08%-41.49%) were accurately labeled (n = 26) (**Table 1**). Accuracy of labeling depended on product type [χ^2 (1) = 16.75; P = .002], with vaporization liquid most frequently mislabeled (21 mislabeled products; 87.50% [95% CI, 69.00%-95.66%]) and oil most frequently labeled accurately (18 accurately labeled products; 45.00% [95% CI, 30.71%-60.17%]). Concentration of unlabeled cannabinoids was generally low (**Table 2**); however, THC was detected (up to 6.43

Table 1. Label Accuracy by Cannabidiol Extract Type

	Cannabidiol Extract Products			
	Oil (n = 40)	Tincture (n = 20)	Vaporization Liquid (n = 24)	Total (N = 84)
Label accuracy, No. of products (%) [95% CI]				
Accurate[a]	18 (45.00) [30.71-60.17]	5 (25.00) [11.19-46.87]	3 (12.50) [4.34-31.00]	26 (30.95) [22.08-41.49]
Under[b]	10 (25.00) [14.19-40.19]	8 (40.00) [21.88-61.34]	18 (75.00) [55.10-88.00]	36 (42.85) [32.82-53.53]
Over[c]	12 (30.00) [18.07-45.43]	7 (35.00) [18.12-56.71]	3 (12.50) [4.34-31.00]	22 (26.19) [17.98-36.48]
Labeled concentration, mg/mL				
Mean (95% CI)	56.15 (14.23-98.07)	11.14 (5.60-16.60)	26.15 (12.50-39.74)	36.86 (16.21-57.51)
Median (range)	22.26 (2.50-800.00)	8.33 (1.33-50.00)	18.33 (2.00-160.00)	15.00 (1.33-800.00)
Deviation of labeled content from tested value, mg/mL				
Mean (95% CI) [% of deviation]	10.34 (4.95-15.74) [29.01]	3.94 (2.74-5.14) [220.62]	11.52 (8.10-14.94) [1098.70]	9.16 (4.96-13.36)[380.26]
Median (range) [% of deviation]	2.76 (0.13-144.73) [12.11]	1.48 (0.01-22.30) [19.12]	4.62 (0.14-66.07) [67.34]	3.17 (0.10-144.73) [20.42]

[a] Cannabidiol content tested within 10% of labeled value.

[b] Cannabidiol content exceeded labeled value by more than 10%.

[c] Cannabidiol content tested more than 10% below labeled value.

Table 2. Observed Cannabinoid Concentration of 84 Tested Extract Products Sold Online

	Average Observed Concentration Across Tests, mg/mL	
Cannabinoid	Mean (SD)	Median (Range)
Cannabidiol[a]	30.96 (80.86)	9.45 (0.10-655.27)
Cannabidiolic acid	1.35 (6.74)	0 (0-55.73)
Cannabigerol	0.08 (0.55)	0 (0-4.67)
Cannabinol	0	0
Δ-9-Tetrahydrocannabinol	0.45 (1.18)	0 (0-6.43)
Δ-9-Tetrahydrocannabibolic acid	0	0

[a] The mean labeled concentration for cannabidiol was 36.86 mg/mL (SD, 96.56) and the median was 15.00 mg/mL (range, 1.33-800.0).

mg/mL) in 18 of the 84 samples tested (21.43% [95% CI, 14.01%-31.35%]), cannabidiolic acid (up to 55.73 mg/mL) in 13 of the 84 samples tested (15.48% [95% CI, 9.28%-24.70%]), and cannabigerol (up to 4.67 mg/mL) in 2 of the 84 samples tested (2.38% [95% CI, 0.65%-8.27%]).

Discussion | Among CBD products purchased online, a wide range of CBD concentrations was found, consistent with the lack of an accepted dose. Of tested products, 26% contained less CBD than labeled, which could negate any potential clinical response. The overlabeling of CBD products in this study is similar in magnitude to levels that triggered warning letters to 14 businesses in 2015-2016 from the US Food and Drug Administration[3] (eg, actual CBD content was negligible or less than 1% of the labeled content), suggesting that there is a continued need for federal and state regulatory agencies to take steps to ensure label accuracy of these consumer products. Underlabeling is less concerning as CBD appears to neither have abuse liability nor serious adverse consequences at high doses[4,5]; however, the THC content observed may be sufficient to produce intoxication or impairment, especially among children.[6] Although the exclusive procurement of products online is a study limitation given the frequently changing online marketplace, these products represent the most readily available to US consumers. Additional monitoring should be conducted to determine changes in this marketplace over time and to compare internet products with those sold in dispensaries. These findings highlight the need for manufacturing and testing standards, and oversight of medicinal cannabis products.

Marcel O. Bonn-Miller, PhD
Mallory J. E. Loflin, PhD
Brian F. Thomas, PhD
Jahan P. Marcu, PhD
Travis Hyke, MS
Ryan Vandrey, PhD

Author Affiliations: University of Pennsylvania Perelman School of Medicine, Philadelphia (Bonn-Miller); Veterans Affairs San Diego Health Care System, San Diego, California (Loflin); RTI International, Research Triangle Park, North Carolina (Thomas); Americans for Safe Access, Washington DC (Marcu); Palo Alto University, Palo Alto, California (Hyke); Johns Hopkins University School of Medicine, Baltimore, Maryland (Vandrey).

Accepted for Publication: August 7, 2017.

Corresponding Author: Marcel O. Bonn-Miller, PhD, University of Pennsylvania Perelman School of Medicine, 3440 Market St, Ste 370, Philadelphia, PA 19104 (mbonn@pennmedicine.upenn.edu).

Author Contributions: Dr Bonn-Miller had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bonn-Miller, Loflin, Thomas, Vandrey.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bonn-Miller, Loflin, Marcu, Vandrey.
Critical revision of the manuscript for important intellectual content: Bonn-Miller, Loflin, Thomas, Hyke, Vandrey.
Statistical analysis: Loflin, Marcu.
Obtained funding: Bonn-Miller.
Administrative, technical, or material support: Bonn-Miller, Loflin, Thomas, Hyke, Vandrey.
Supervision: Bonn-Miller.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Bonn-Miller, Thomas, and Vandrey reported serving as unpaid board members of the Institute for Research on Cannabinoids. Dr Bonn-Miller reported receiving personal fees from Zynerba Pharmaceuticals, the Lambert Center for the Study of Medicinal Cannabis and Hemp, the Realm of Caring Foundation, Tilray, CW Botanicals, Insys Therapeutics, International Cannabis and Cannabinoids Institute, the Medical Cannabis Institute, and Aphria. Dr Vandrey reported receiving personal fees from Zynerba Pharmaceuticals, CW Hemp, Battelle Memorial Institute, and Insys Pharmaceuticals. No other disclosures were reported.

1. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA*. 2015;313(24):2456-2473.

2. Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO. Cannabinoid dose and label accuracy in edible medical cannabis products. *JAMA*. 2015;313(24):2491-2493.

3. US Food and Drug Administration. 2016 Warning letters and test results for cannabidiol-related products. https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm. Accessed August 15, 2017.

4. Babalonis S, Haney M, Malcolm RJ, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend*. 2017;172:9-13.

5. Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a *Cannabis sativa* constituent. *Curr Drug Saf*. 2011;6(4):237-249.

6. Crippa JA, Crippa AC, Hallak JE, Martín-Santos R, Zuardi AW. Δ9-THC intoxication by cannabidiol-enriched cannabis extract in two children with refractory epilepsy. *Front Pharmacol*. 2016;7:359.

Cannabis Pharmacology: The Usual Suspects and a Few Promising Leads

Ethan B. Russo[*,1], **Jahan Marcu**[†]
*PHYTECS, Los Angeles, CA, United States
[†]Americans for Safe Access, Patient Focused Certification, Washington, DC, United States
[1]Corresponding author: e-mail address: erusso@phytecs.com

Contents

Advances in Pharmacology
ISSN 1054-3589
http://dx.doi.org/10.1016/bs.apha.2017.03.004

Abstract

The golden age of cannabis pharmacology began in the 1960s as Raphael Mechoulam and his colleagues in Israel isolated and synthesized cannabidiol, tetrahydrocannabinol, and other phytocannabinoids. Initially, THC garnered most research interest with sporadic attention to cannabidiol, which has only rekindled in the last 15 years through a demonstration of its remarkably versatile pharmacology and synergy with THC. Gradually a cognizance of the potential of other phytocannabinoids has developed. Contemporaneous assessment of cannabis pharmacology must be even far more inclusive. Medical and recreational consumers alike have long believed in unique attributes of certain cannabis chemovars despite their similarity in cannabinoid profiles. This has focused additional research on the pharmacological contributions of mono- and sesquiterpenoids to the effects of cannabis flower preparations. Investigation reveals these aromatic compounds to contribute modulatory and therapeutic roles in the cannabis entourage far beyond expectations considering their modest concentrations in the plant. Synergistic relationships of the terpenoids to cannabinoids will be highlighted and include many complementary roles to boost therapeutic efficacy in treatment of pain, psychiatric disorders, cancer, and numerous other areas. Additional parts of the cannabis plant provide a wide and distinct variety of

other compounds of pharmacological interest, including the triterpenoid friedelin from the roots, canniprene from the fan leaves, cannabisin from seed coats, and cannflavin A from seed sprouts. This chapter will explore the unique attributes of these agents and demonstrate how cannabis may yet fulfil its potential as Mechoulam's professed "pharmacological treasure trove."

ABBREVIATIONS

BCP beta-caryophyllene
CB_1 cannabinoid type 1 receptor
CB_2 cannabinoid type 2 receptor
DEA Drug Enforcement Agency
DEET *N,N*-dimethyl-toluamide
ECS endocannabinoid system
EO essential oil
FEMA Flavor and Extract Manufacturers' Association
GRAS Generally Recognized As Safe
GVHD graft-vs-host-disease
MAGL monoacylglycerol lipase
MRSA methicillin-resistant *Staphylococcus aureus*
NAAA *N*-acylethanolamine-hydrolyzing acid amidase
PPARγ peroxisome proliferator-activated receptor gamma
TRP transient receptor potential
TRPA1 TRP ankyrin-type 1

1. INTRODUCTION

Mammals and plants are exposed to cannabinoids and related compounds that notably modulate their growth and physiology. The human species in the Old World grew up around the >70 million-year-old cannabis plant, giving us a natural affinity to cannabinoids (Clarke & Merlin, 2012). This plant has been documented as a provider of food, clothing, textiles, and medicine for millennia. For thousands of years, the plant has been associated with relieving symptoms of disease and has demonstrated numerous therapeutic properties (Russo, 2007, 2011).

In this century, we are finally beginning to understand the precise pharmacological mechanisms underlying the effects of cannabis and related preparations, most of which can be explained through the endocannabinoid system (ECS). As perhaps the most significant human biological scientific discovery in the last 30 years, the ECS is only now being integrated into medical school curricula.

Analytical chemistry has revealed a rich and abundant "pharmacological treasure trove" in the plant. Compounds that may affect the pharmacology of cannabinoids are abundant in nature, and so we may dangerously and mistakenly consider their presence to be trivial. If so, this could cause us to lose sight of the subtlety and efficiency of their design when applied in combination. There are some 100 clinical studies and thousands of articles on the pharmacology and pharmacodynamics of cannabis and its influence on how humans eat, sleep, heal, and learn.

In this review, we hope to demystify some of the wonder of cannabis as a medicine by providing a concise overview of the pharmacological mechanisms of cannabis compounds, which will hopefully guide medical school curricula, advances in therapies, and lead to changes in public health approaches both nationally and internationally. As government information sources are updated with cannabis research conducted in the current century, the future of cannabis in society will depend strongly on how well we understand this plant, of which our access to for research and medicine currently floats on the winds of politics (Fig. 1).

2. CANNABIS PHYTOCANNABINOIDS (FIG. 2)

2.1 Tetrahydrocannabinol

The pharmacology of tetrahydrocannabinol (THC) is perhaps the most well studied of any scheduled substance, having well over 100 published clinical studies of medical cannabis and related products which contain THC (Ben Amar, 2006; Hazekamp & Grotenhermen, 2010; Kowal, Hazekamp, & Grotenhermen, 2016; Marcu, 2016; Pertwee & Cascio, 2014; Russo & Hohmann, 2012). THC, among a pantheon of over 100 (Hanus, Meyer, Munoz, Taglialatela-Scafati, & Appendino, 2016), is the most common phytocannabinoid in cannabis drug chemotypes, and is produced in the plant via an allele codominant with CBD (de Meijer et al., 2003). THC displays both cannabinoid receptor-dependent and -independent mechanisms.

THC interacts efficiently with CB_1 ($K_i = 5.05–80.3$ nM) and CB_2 receptors ($K_i = 1.73–75.3$ nM), which underlies its activities in modulating pain, spasticity, sedation, appetite, and mood (Russo, 2011). Additionally, it is a bronchodilator (Williams, Hartley, & Graham, 1976), neuroprotective antioxidant (Hampson, Grimaldi, Axelrod, & Wink, 1998), antipruritic agent in cholestatic jaundice (Neff et al., 2002) and has 20 times the antiinflammatory power of aspirin and twice that of hydrocortisone (Evans, 1991). THC is likely to avoid potential pitfalls of either COX-1

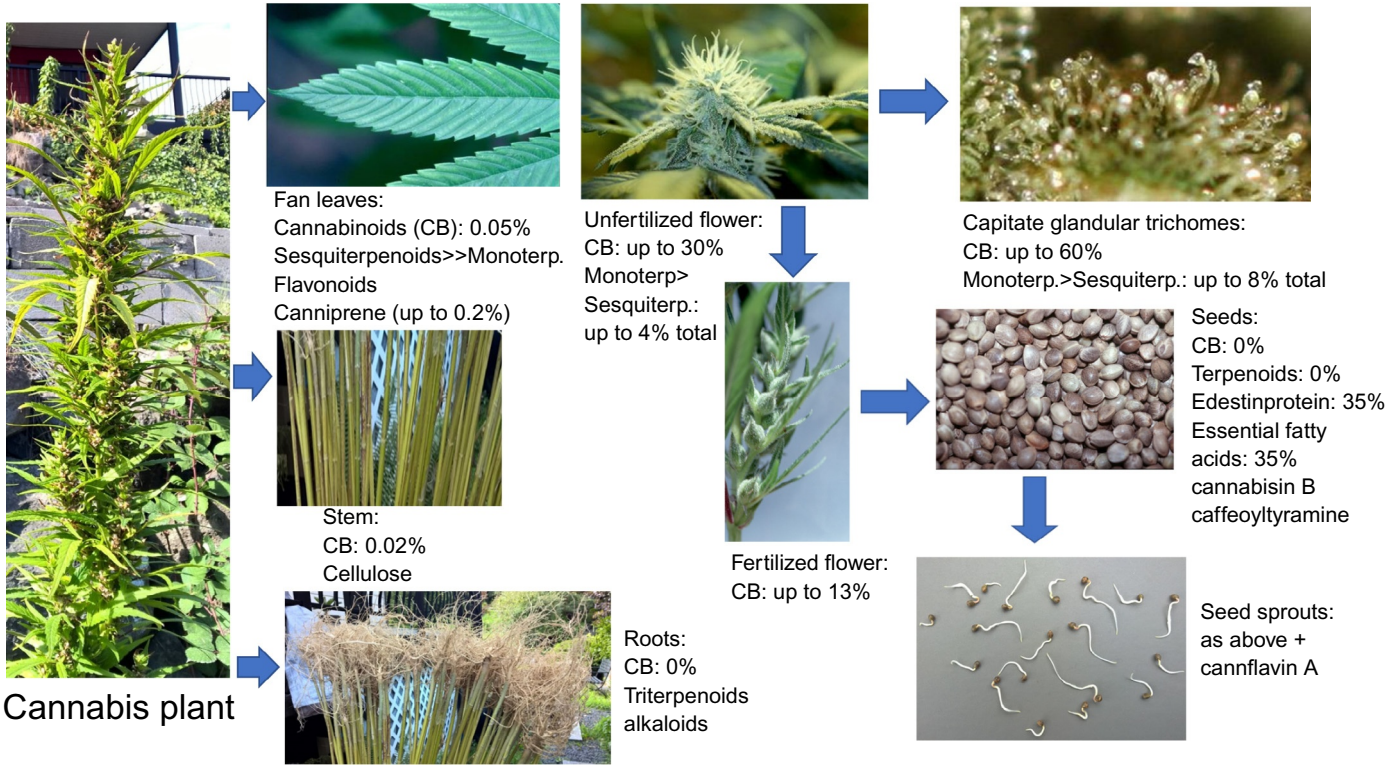


Fig. 1 The cannabis plant, its parts, and their phytochemical components. Component percentages are based on information from Callaway (2004), (Meier & Mediavilla, 1998) and Potter (2009) (all photos by EBR).

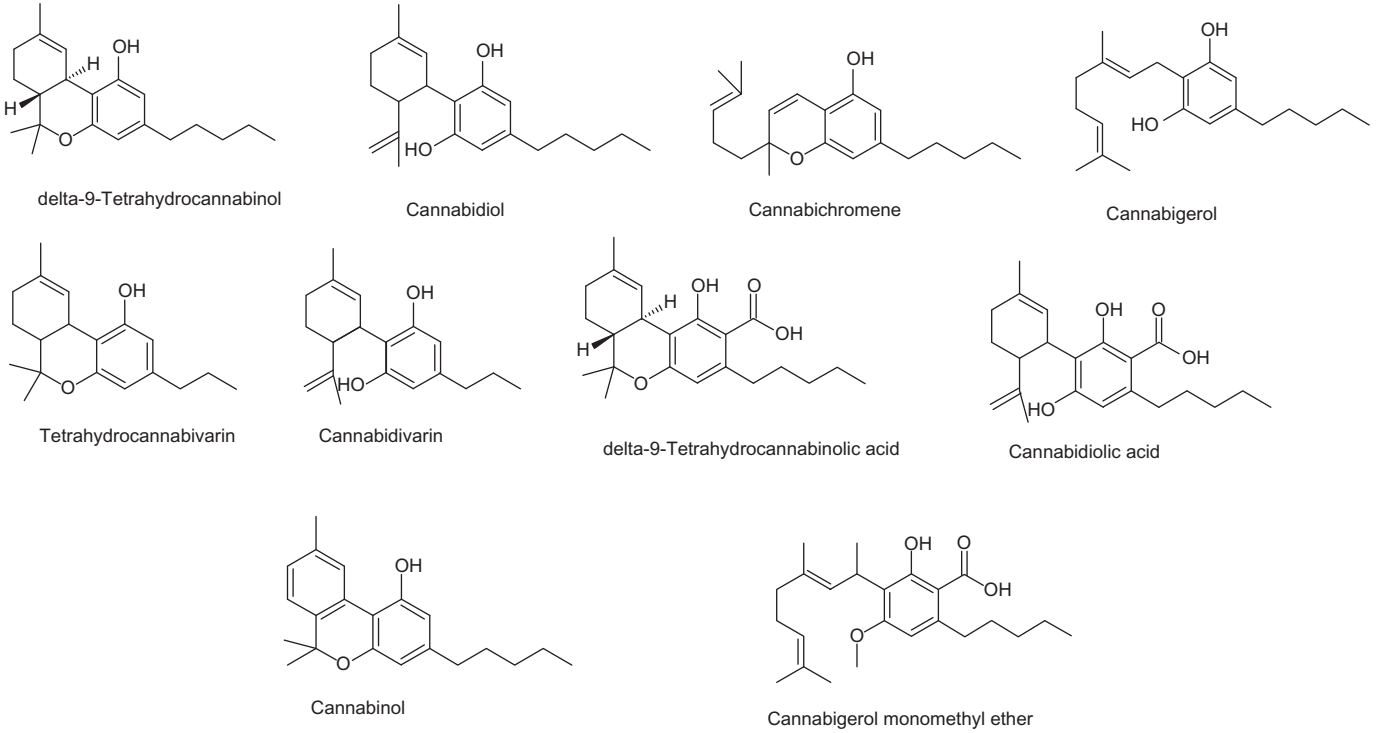


Fig. 2 Phytocannabinoids commonly encountered in cannabis (all structures drawn by EBR using ChemSketch 2015.2.5).

or COX-2 inhibition, as such activity is only noted at concentrations far above those attained therapeutically (Stott, Guy, Wright, & Whittle, 2005).

While THC stimulates both CB_1 and CB_2 receptors, the role and distribution of these two proteins is distinct. Stimulation of CB_1 receptors by THC can lead to a tetrad of effects in assays with laboratory animals; these effects include: suppression of locomotor activity, hypothermia, catalepsy (ring test), and antinociceptive effects in the tail flick test (Martin et al., 1991). CB_2 receptor stimulation is associated with pain relief and antiinflammatory activities (Pacher & Mechoulam, 2011), but it is not associated with other CB_1 effects such as appetite stimulation.

2.1.1 THC Mechanisms at CB_1 and CB_2

THC-mediated CB_1 receptor stimulation inhibits forskolin-stimulated adenylate cyclase (AC) and leads to the inhibition N-, Q-, L-type calcium channels. Ion channels can be modulated from CB_1 receptor stimulation. For example, CB_1 receptor stimulation releases G proteins to activate inwardly rectifying potassium channels, which may be induced by a variety of CB_1 partial agonists (Console-Bram, Marcu, & Abood, 2012). This receptor signaling also stimulates the activity of MAP kinases. MAP kinase pathways are often activated by GPCRs and can alter the activity of ERK1/2, c-Jun N-terminal kinase (JNK), p38 MAP kinase, and/or ERK5 proteins. The stimulation of their activity can control cell growth and their metabolism.

CB_1 localization is widespread, and the distribution parallels the known pharmacological actions of THC; the locations of CB_1 receptors make them a good therapeutic target (Herkenham et al., 1990; Pacher, 2006; Russo, 2016a). CB_1 has particularly high expression in neuronal tissue, specifically in pre- and postsynaptic neurons in the central nervous system (CNS). CB_1 protein is found in the nucleus of solitary tract (i.e., antiemetic effects), hypothalamus, motor systems, motor cortex, basal ganglia, cerebellum, spinal cord (motor neurons in spinal cord), eye, sympathetic ganglia (also enteric nervous system), immune system (bone marrow, thymus, spleen, tonsils), breast cancer cell lines, and other peripheral sites such as the heart, lungs, adrenals, kidneys, liver, colon, prostrate pancreas, testes, ovaries, and placenta.

THC-mediated CB_2 receptor stimulation leads to inhibition of forskolin-stimulated AC activation and stimulating MAP kinases but lack the effects on ion channels of CB_1. CB_2 is localized mainly in cells of the immune system, such as bone marrow, thymus, spleen, tonsils, T and B lymphocytes, monocytes, NK cells, PMN, and mast cells. The levels of CB_2 expression increase during activation/differentiation of immune cells. During inflammation or injury, the number of CB_2 receptors available for

stimulation increases significantly. CB_2 is also found in tissue of the uterus, lung, bone (osteoclasts, osteoblasts, osteocytes), microglia, and brainstem neurons. CB_2 DNA mutations or polymorphisms are associated with osteoporosis in human populations, and strains of mice that are engineered without CB_2 can have accelerated age-related trabecular bone loss.

The maximal effect of THC at the CB receptor proteins is well below that of synthetic cannabinoids (i.e., nabilone, HU-210, JWH-018, etc.). Hence, THC, as well as anandamide, are classified as partial agonists because other ligands or cannabinoids exist, which are much more potent at cannabinoid receptors (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990; Pacher, 2006). For example, 11-hydroxy metabolites of THC that are generated by the liver from oral administration of THC interact more efficiently at CB_1 receptors. It should also be noted that cannabinoid drugs with equal (i.e., Marinol®) or greater (i.e., nabilone) potency than THC, have been approved and available by prescription for decades, but no significant black market exists for these expensive and hard to obtain standardized preparations nor has addiction treatment been a significant issue for these cannabis-based medicines (Calhoun, Galloway, & Smith, 1998; Robson, 2011).

2.1.2 THC Activity Independent of CB_1 and CB_2

THC has been reported to interact with a wide variety of proteins including various receptors, channels, and enzymes. These pharmacological actions of THC are well documented in biochemical and mammalian research studies. Findings and research demonstrating actions of THC above 10 μM concentration are beyond the scope of this chapter as beyond this concentration, the results become difficult to interpret as far as what the physiological significance could be.

2.1.3 Receptors and Channels

At <1 μM THC can activate GPR18, GPR55, peroxisome proliferator-activated receptor gamma (PPARγ) nuclear receptors, as well as TRPA1 and TRPV2 cation channels, while enhancing the activity of non-CB receptors on sensory neurons mediating the release of calcitonin gene-related peptide (an effector in migraine attacks) and potentiating glycine-ligated ion channels (important for pain relief) (Hong & Liu, 2017). Conversely, THC blocks or antagonizes the activity of $5\text{-}HT_{3A}$ ligand-gated ion and TRPM8 cation channel at <1 μM.

Between 1 and 10 μM, THC can activate the PPARγ nuclear receptor, TRPV3 and TRPV4 cation channels, and potentiate the activity of β-adrenoceptors. THC can either block or activate GPR55 at these

concentrations, depending on experimental conditions. Perhaps most relevant to current clinic and public health issues is the ability of THC to displace opiates from the μ-opioid receptor, as well as allosterically modulate the μ- and δ-opioid receptor to inhibit their activity between 1 and 10 μM (Lichtman, Sheikh, Loh, & Martin, 2001; Pertwee et al., 2010). This perhaps underlies the potential of cannabis as part of a viable solution to the opiate crisis in terms of treating addiction, withdrawal, and harnessing the benefits of cannabinoid-opiate coadministration in the clinic (Americans for Safe Access, 2016). When THC and morphine are coadministered, ¼ the dose of morphine is required to reach significant reductions in pain (Naef et al., 2003).

Conversely, THC inhibits T-type calcium (Cav3) voltage-gated ion channels, potassium Kv1.2 voltage-gated ion channels, conductance in Na^+ voltage-gated ion channels (−), and conductance in gap junctions between cells at concentrations between 1 and 10 μM. THC can also interact with a variety of enzymes such as phosphlipases, lysophosphatidylcholine acyl transferase, lipoxygenase, Na^+-K^+-ATPase, Mg^{2+}-ATPase, CYP1A1, CYP1A2, CYP1B1, CYP2B6, CYP2C9, and monoamine oxidase activity (Evans, 1991; Pertwee, 1988; Pertwee & Cascio, 2014; Yamaori et al., 2012; Yamaori, Kushihara, Yamamoto, & Watanabe, 2010; Yamaori, Okamoto, Yamamoto, & Watanabe, 2011). The synaptic conversion of tyrosine to noradrenaline and dopamine (DA) is increased by THC while norepinephrine-induced melatonin biosynthesis is inhibited.

Recently, THC has shown significant benefits in helping to reduce complications during organ transplant and in graft-vs-host-disease (GVHD) in mammals. The research on THC in GVHD and transplant has already affected public policy in California, where cannabis use no longer constitutes grounds for being dismissed from transplant waiting list. The perceived pharmacological effects of THC may also be dependent on diet of the mammal (Balvers et al., 2012; Lafourcade et al., 2011; Lowette, Roosen, Tack, & Berghe, 2015), due to the fact that anandamide and endocannabinoids are derived in vivo from omega-3 and -6 fatty acid intake and their dietary deficiency could lead to uncoupling of G protein-coupled receptors.

2.2 Cannabidiol

The main nonintoxicating phytocannabinoids are cannabidiol (CBD) and its acidic precursor cannabidiolic acid. These are the most abundant phytocannabinoids in European hemp (Upton et al., 2013). CBD has a very low affinity for CB receptors but may have significant CB_1- and

CB_2-independent mechanisms of action and possess the unique ability to antagonize CB_1 at very low concentrations when in the presence of THC (Thomas et al., 2007). This observed antagonism may be related to CBD's ability to act as a negative allosteric modulator at CB_1 receptors (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015).

CBD is reported to be an agonist at TRPV1 (Bisogno et al., 2001) and 5-HT_{1A} receptors (Russo, Burnett, Hall, & Parker, 2005) and to enhance adenosine receptor signaling (Carrier, Auchampach, & Hillard, 2006). Exceptional tolerability of CBD in humans has been demonstrated (Mechoulam, Parker, & Gallily, 2002). CBD can produce a wide range of pharmacological activity including anticonvulsive, antiinflammatory, antioxidant, and antipsychotic effects. These effects underlie the neuroprotective properties of CBD and support its role in the treatment of a number of neurological and neurodegenerative disorders, including epilepsy, Parkinson disease, amyotrophic lateral sclerosis, Huntington disease, Alzheimer disease, and multiple sclerosis (de Lago & Fernández-Ruiz, 2007; Hofmann & Frazier, 2013; Martin-Moreno et al., 2011; Scuderi et al., 2009).

CBD possesses the unique ability to counteract the intoxicating and adverse effects of cannabis, such as anxiety, tachycardia, hunger, and sedation in rats and humans (Murillo-Rodriguez, Millan-Aldaco, Palomero-Rivero, Mechoulam, & Drucker-Colin, 2006; Nicholson, Turner, Stone, & Robson, 2004; Russo, 2011; Russo & Guy, 2006). The benefits of CBD include reducing the unwanted side effects of THC, a dynamic pharmacological effect that has been fairly well studied in clinical trials. CBD is included in a specific ratio of 1:1 in the medicinal cannabis preparation and licensed pharmaceutical known as Sativex®, which has been studied in numerous properly controlled clinical trials representing thousands of patient/years of data (Flachenecker, Henze, & Zettl, 2014; Rog, Nurmiko, Friede, & Young, 2005; Sastre-Garriga, Vila, Clissold, & Montalban, 2011; Wade, Collin, Stott, & Duncombe, 2010).

Recently, CBD demonstrated its strong antiinflammatory and immunosuppressive properties in a phase II study on GVHD (Yeshurun et al., 2015). CBD (300 mg/day) starting a week before the procedure was associated with less mortality and complications.

There is recent report that CBD isomerizes to THC under acidic conditions in vitro, but there is no evidence that directly supports that this is actually occurring in humans (Deiana et al., 2012; Grotenhermen, Russo, & Zuardi, 2017; Russo, 2017).

2.3 Cannabigerol

This compound was purified from cannabis the same year as THC (Gaoni & Mechoulam, 1964), but cannabigerol (CBG) lacks its psychotropic effects (Grunfeld & Gresty, 1998; Grunfeld & Edery, 1969). Normally, CBG appears as a relatively low concentration intermediate in the plant, but recent breeding work has yielded cannabis chemotypes lacking in downstream enzymes that express 100% of their phytocannabinoid content as CBG (de Meijer & Hammond, 2005; de Meijer, Hammond, & Micheler, 2009). CBG, the parent phytocannabinoid compound, has a relatively weak partial agonistic effect at CB_1 (K_i 440 nM) and CB_2 (K_i 337 nM) (Gauson et al., 2007).

CBG may stimulate a range of receptors important for pain, inflammation, and heat sensitization. This compound can antagonize TRPV8 receptors and stimulates TRPV1, TRPV2, TRPA1, TRPV3, TRPV4, and α2-adrenoceptor activity (Cascio, Gauson, Stevenson, Ross, & Pertwee, 2010; De Petrocellis & Di Marzo, 2010; De Petrocellis et al., 2011). It is a relatively potent TRPM8 antagonist for possible application in prostate cancer and detrusor overactivity and bladder pain (De Petrocellis & Di Marzo, 2010; Mukerji et al., 2006). CBG can also antagonize the stimulation of serotonin 5-HT_{1A} and CB_1 receptors with significant efficiency. Older work supports gamma aminobutyric acid (GABA) uptake inhibition greater than THC or CBD that could suggest muscle relaxant properties (Banerjee, Snyder, & Mechoulam, 1975).

Analgesic and antierythemic effects and the ability to block lipooxygenase were said to surpass those of THC (Evans, 1991). CBG demonstrated modest antifungal effects (ElSohly, Turner, Clark, & Eisohly, 1982). CBG has remarkable anticancer properties in basic research models, it has proved to be an effective cytotoxic in high dosage on human epithelioid carcinoma and is one of the more effective phytocannabinoids against breast cancer (Baek et al., 1998; Ligresti et al., 2006). CBG has significant antidepressant effects in the rodent tail suspension model and is a mildly antihypertensive agent (Maor, Gallily, & Mechoulam, 2006; Musty & Deyo, 2006). Additionally, CBG inhibits keratinocyte proliferation suggesting utility in psoriasis (Wilkinson & Williamson, 2007).

CBG is a strong AEA uptake inhibitor and a powerful agent against MRSA (methicillin-resistant *Staphylococcus aureus*) (Appendino et al., 2008; De Petrocellis et al., 2011). Finally, CBG behaves as a potent α2-adrenoreceptor agonist, supporting analgesic effects previously noted, and moderate 5-HT_{1A} antagonist suggesting antidepressant properties (Cascio et al., 2010; Formukong, Evans, & Evans, 1988).

2.4 Cannabichromene

Cannabichromene (CBC) was first reported to be isolated by two groups, using either a hexane/florisil extraction method from hashish or a benzene percolation of hemp (Claussen, Von Spulak, & Korte, 1966; Gaoni & Mechoulam, 1966). This cannabinoid represents ~0.3% of constituents from confiscated cannabis, and it is important to note that varieties and preparations exist in the commercial and medical markets with significantly higher content (de Meijer & Limited, 2011; Mehmedic et al., 2010; Meijer, Hammond, & Micheler, 2008; Swift, Wong, Li, Arnold, & McGregor, 2013). CBC-rich cannabis strains are the result of selecting for the inheritance of a recessive gene, achievable through extensive cross-breeding. CBC or CBC-like derivatives have also been found in *Rhododendron anthopogonoides*, at the time of this writing, this species and its extracts are not listed under the list of scheduled drugs by the DEA (Iwata & Kitanaka, 2011).

CBC can interact with transient receptor potential (TRP) cation channels that inhibit endocannabinoid inactivation, and stimulate CB_2 receptors ($K_i \sim 100$ nm), but it does not have significant activity at CB_1 receptors ($K_i > 1$ μM) (De Petrocellis et al., 2011, 2012, 2008; Shinjyo & Di Marzo, 2013). TRP channels and the ECS are involved in inflammation and have a role in pain. In mice, CBC can relieve pain, potentiate the analgesic effects of THC, ameliorate-induced colonic inflammation, and paw edema by demonstrably inhibiting macrophage and MAGL activity (Cascio & Pertwee, 2014; Davis & Hatoum, 1983; Maione et al., 2011).

The mechanism underlying CBC's observed effects in mammals is supported by pharmacodynamic studies (De Petrocellis et al., 2008; Ligresti et al., 2006; Romano et al., 2013). These have shown that CBC can stimulate TRP ankyrin-type 1 (TRPA1) cation channels ($EC_{50} = 90$ nM), and desensitize these channels ($IC_{50} = 370$ nM). Further evidence for the role of CBC in inflammation includes the compounds ability to interact with TRPV4 and TRPV3 cation channels ($EC_{50} = 600$ nM and 1.9 μM, respectively), and desensitize TRPV2 and TRPV4 ($IC_{50} = 6.5$ and 9.9 μM, respectively) (Cascio & Pertwee, 2014; De Petrocellis et al., 2012). Beyond inflammation and pain, CBC may have a positive effect on the viability of mammalian adult neural stem cell progenitor cells, which are an essential component of brain function in health and disease (Shinjyo & Di Marzo, 2013).

In summary, CBC can be one of the most abundant nonintoxicating CBs found in cannabis, due to a recessive gene (Brown & Harvey, 1990; Holley, Hadley, & Turner, 1975). CBC can cause strong antiinflammatory

effects in animal models of edema through non-CB receptor mechanisms (DeLong, Wolf, Poklis, & Lichtman, 2010). CBC has been shown to significantly interact with TRP cation channels, including TRPA1, TRPV1–4, and TRPV8 (Pertwee & Cascio, 2014). CBC can also produce behavioral activity of the cannabinoid tetrad. The effects of CBC, particularly nociception in animal models, can be augmented for additive results when THC is co-administered.

2.5 Cannabinol

Cannabinol (CBN) is the nonenzymatic oxidation byproduct of THC and is most commonly an artifact found after prolonged storage, especially at higher temperatures. CBN was the first cannabinoid to be identified and isolated from cannabis (Wood, Spivey, & Easterfield, 1899). This discovery was most likely due to rampant degradation of THC to CBN due to poor quality control, the transportation and storage conditions related to the 19th century; challenges that are still difficult to overcome in existing cannabis products (Upton et al., 2013).

Relative to THC, CBN maintains about ¼ the potency (K_i at $CB_1 = 211.2$ nM, $CB_2 = 126.4$ nM) (Rhee et al., 1997). CBN can be sedative, anticonvulsant in animal and human studies, and has demonstrated significant properties related to antiinflammatory, antibiotic, and anti-MRSA activity (minimum inhibitory concentration (MIC) 11 μg/mL) (Appendino et al., 2008; Evans, 2007; McPartland & Russo, 2001; Musty, Karniol, Shirikawa, Takahashi, & Knobel, 1976; Turner, Elsohly, & Boeren, 1980).

CBN has potential as a component in topical applications, inhibiting keratinocyte proliferation (low micromolar) via CBR-independent mechanisms, suggesting utility in psoriasis (Wilkinson & Williamson, 2007). Beyond cannabinoid proteins, the compound has TRPV2 (high-threshold thermosensor) agonistic effects (EC_{50} 77.7 μM), which are of interest in possible topical applications in treating burns (Qin et al., 2008; Russo, 2014). A review of phytocannabinoids summarized the ability of CBN to inhibit the activity of a number of enzymes, including cyclooxygenase, lipoxygenase, and a host of cytochrome P450 (CYP) enzymes (e.g., CYP1A1, CYP1A2, CYP2B6, CYP2C9, CYP3A4, CYP3A5, CYP2A6, CYP2D6, CYP1B1, and CYP3A7) (Pertwee & Cascio, 2014). CBN may also stimulate the activity of phospholipases. CBN additionally stimulates recruitment of quiescent mesenchymal stem cells in marrow (10 μM) promoting bone formation (Scutt & Williamson, 2007) and can affect breast cancer resistance proteins (IC_{50} approximately 145 μM) (Holland, Allen, & Arnold, 2008).

2.6 Tetrahydrocannabivarin

Tetrahydrocannabivarin (THCV) is a propyl analogue of THC most often encountered in low concentration in dried plant material, but in THCV-rich plants up to 16% THCV by dry weight has been recorded (Meijer & Hammond, 2005). Mechanistically speaking, THCV can behave as both an agonist and an antagonist at CB_1 receptors depending on the concentration (Pertwee, 2008). THCV produces weight loss, and decreases body fat and serum leptin concentrations with increased energy expenditure in obese mice (Cawthorne, Wargent, Zaibi, Stott, & Wright, 2007; Riedel et al., 2009). THCV also demonstrates prominent anticonvulsant properties in rodent cerebellum and pyriform cortex (Hill et al., 2010). THCV appears as a fractional component of many southern African cannabis chemotypes, although plants highly predominant in this agent have been produced (de Meijer et al., 2003; de Meijer & Hammond, 2016). THCV has the CB_2-based ability to suppress carageenan-induced hyperalgesia and inflammation, and both phases of formalin-induced pain behavior via CB_1 and CB_2 in mice (Bolognini et al., 2010).

Antagonizing CB_1 receptors can suppress appetite and the intoxicating effects of THC. However, caution must be emphasized when developing CB_1 receptor antagonists. Clinical studies in human populations studying the antagonists of CB_1 receptors with the drug rimonabant (SR141716A) led to depressive episodes and potentially worsened neurodegenerative disease outcomes, and ultimately this drug was withdrawn from the market (McLaughlin, 2012). Despite this setback, SR141716A remains a very important research tool for unlocking potential medical treatments targeting the CB receptors and deepening the understanding of the ECS. Importantly, the neutral antagonism mechanism of action of THCV seems to be free of the adverse events associated with the CB_1 inverse agonists (McPartland, Duncan, Di Marzo, & Pertwee, 2015).

2.7 Tetrahydrocannabinolic Acid

Cannabinoid acids are found as primary metabolites in cannabis plants. For example, tetrahydrocannabinol acid (THCA-A) is synthesized in glandular trichomes of the cannabis plant and forms THC after the parent compound is decarboxylated by UV exposure, prolonged storage, or heat (Moreno-Sanz, 2016). THCA-A can represent up to 90% of total THC content in the plant, it has about 70% conversion rate into THC when smoked (Dussy, Hamberg, Luginbuhl, Schwerzmann, & Briellmann, 2005): decarboxylation of THCA to THC is incomplete even at high temperatures in gas

chromatography. Additionally, THCA can be detected in serum, urine, and oral fluid of cannabis consumers up to 8 h after smoking (Jung, Kempf, Mahler, & Weinmann, 2007). The cannabinoid acids do not produce any significant or documented psychotropic effects. THCA-A is the immediate natural precursors of THC. THCA-A is one the primary phytocannabinoid metabolites and can cause apoptosis of insect cells (Sirikantaramas et al., 2004).

THCA-A is reported to be a weak agonist of CB_1 and CB_2 receptors compared with THC (K_i CB1 = 630 vs 3.5 nM; K_i CB_2 = 890 vs 3.2 nM) (Verhoeckx et al., 2006). In other laboratories, THCA-A effectively bound to both cannabinoid receptors, displaying a higher affinity for CB_1, with K_i values of 23.51–3.5 and 56.13–8.2 nM, respectively. In fact, THCA-A (log IC_{50} = 1.793 ± 0.00) and THC (log IC_{50} = 1.941–0.01) displaced CP-55,940 from CB_1 in a similar range of concentrations (Rosenthaler et al., 2014).

THCA-A attenuated nausea-induced gaping in rats and vomiting in shrews through a mechanism that required CB_1 activation, which is reversible with a CB_1 receptor antagonist (Rock, Kopstick, Limebeer, & Parker, 2013). The authors provide additional evidence that this observed effect of THCA-A is not due to the conversion of THCA-A to THC. The effects of THCA-A appear to be partially mediated through cannabinoid receptors, without any reported psychotropic effects associated with THC. The evidence suggests that THCA-A is restricted to the periphery with limited access to the CNS through the blood brain barrier (BBB). This is probably due the presence of a carboxylic acid on THCA-A; such polar residues decrease CNS penetration through the ATP-binding cassette family of transporters (Moreno-Sanz et al., 2013). In fact, brain disposition has been reported for several cannabinoids, but not THCA-A (Alozie, Martin, Harris, & Dewey, 1980; Deiana et al., 2012).

THCA-A can inhibit the release of tumor necrosis factor-alpha (TNF-α) (Verhoeckx et al., 2006), can efficiently interact with TRPM8 channels and can stimulate or desensitize a range of other TRP cation channels. THCA-A has been found to inhibit enzymes responsible for the breakdown of endocannabinoids, as well as COX-1 and -2, thus stimulating the ECS by increasing levels of endogenous cannabinoids. In a basic model of Parkinson's disease, THCA-A (10 μM) increased cell survival and significantly ameliorated altered neurite morphology (Moldzio et al., 2012). THCA-A reduces cell viability of various cancer cell lines when administered in vitro (Moreno-Sanz, 2016). Basic research has conclusively shown that THCA-A can have immunomodulatory, antiinflammatory, neuroprotective and antineoplastic activity.

2.8 Cannabidivarin

Cannabidivarin (CBDV) was probably first reported in a benzene extract from a Thai cannabis variety referred to as "Meao" (Shoyama, Hirano, Makino, Umekita, & Nishioka, 1977). Oral CBDV (60 mg/kg) administered to rats can cross the BBB (Deiana et al., 2012). CBDV is capable of activating and blocking, depending on experimental conditions, a diverse number of cation channels. At less than <1 μM TRPA1, TRPM8, and TRPV4 are influenced by CBDV, while around 1–10 μM affects the activity of TRVP1, TRVP2, and TRVP3 cation channels. In addition to cationic influences, this propyl analogue of CBD engages the ECS by inhibiting endocannabinoid degradation at 10 μM through modulating the rate of diacylglycerol lipase activity and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA), the effects of which could magnified with CBDV's ability to inhibit the cellular uptake of anandamide (Pertwee & Cascio, 2014). CBDV also possess the potential for the treatment of nausea and vomiting (Rock, Sticht, & Parker, 2014). There is strong evidence that CBDV has significant anticonvulsant properties, which may rival CBD's therapeutic potential in treating epilepsy, particularly seizures of partial onset (focal seizures) (Williams, Jones, & Whalley, 2014).

2.9 Cannabidiolic Acid

Cannabidiolic acid (CBDA) is the natural precursor or CBD, and this acidic phytocannabinoid can target GPR55, TRPA1, TRPV1, and TRPM8 at concentrations between 1 and 10 μM. At higher concentrations, the compound can inhibit ECS degradation enzymes. CBDA can inhibit by COX-1 and COX-2 (Takeda, Misawa, Yamamoto, & Watanabe, 2008). CBDA also shares CBD's ability to enhance 5-HT_{1A} receptor activation but the acidic compound does not interact efficiency with CB_1 receptors as either an agonist or antagonist (Bolognini et al., 2013; McPartland et al., 2015). The affinity at 5-HT_{1A} for CBDA is greater than an order of magnitude higher compared to CBD. Evidence from animals demonstrates significant antiemetic effects from CBDA (10 or 200 mg/kg ip) (Moreno-Sanz, 2016; Rock & Parker, 2015).

2.10 Cannabigerol Monomethyl Ether

This phytocannabinoid is commonly encountered in cannabis, but has not been researched for pharmacological activity. It is included here to highlight that its presence with relative frequency supports its investigation as a research priority.

3. CANNABIS TERPENOIDS

Terpenoids are aromatic compounds that fulfill unique ecological roles for plants in protection from predation, attraction of pollinators, and myriad other roles (Elzinga, Fischedick, Podkolinski, & Raber, 2015; Fischedick, Hazekamp, Erkelens, Choi & Verpoorte, 2010; McPartland & Russo, 2001, 2014; Russo, 2011). Two excellent general references are Baser and Buchbauer (2016) and Langenheim (1994). They are typically produced in dedicated structures, which in the case of cannabis are the glandular trichomes, the same source of phytocannabinoid production (Potter, 2009). Typically, many are produced by a given plant and form its essential oil (EO). In cannabis, the biochemical diversity of these components is remarkable, with as many as 200 described, although some are artifacts of steam distillation (Lawless, 1995). The biochemical profile of terpenoids in a given plant is more genetically than environmentally determined (Franz & Novak, 2010).

Whereas, the biosynthetic enzymes for phytocannabinoids have been identified for several years, it was only recently that several terpenoid synthases were analyzed in cannabis (Booth, Page & Bohlmann, 2017). Regulation of terpenoid and cannabinoid production in the plant remain important research priorities.

A great deal of debate has surrounded the relative importance, or lack thereof, of cannabis terpenoids to the pharmacological effects of the plant. Despite existing at seemingly low concentrations in a preparation, they have proven to be potent: small amounts in ambient air produce marked behavioral effects to increase or decrease activity levels in rodents, even when observed serum levels are low or negligible (Buchbauer, Jirovetz, Jager, Plank & Dietrich, 1993). Their physiological mechanisms are protean particularly in the CNS, attributable to their lipophilicity, and include effects on ion channels, neurotransmitter, odorant, and tastant receptors, among others (Buchbauer, 2010). Terpenoids, particularly monoterpenoids, are highly bioavailable via inhalation (Falk, Hagberg, Lof, Wigaeus-Hjelm, & Wang, 1990; Falk, Lof, Hagberg, Hjelm, & Wang, 1991; Falk-Filipsson, Lof, Hagberg, Hjelm, & Wang, 1993).

Terpenoid concentrations in cannabis flowers were previously commonly reported in the 1% range, but up to 10% within trichomes (Potter, 2009), but this situation has changed due to selective breeding, such that flower concentrations of 3.5% (Fischedick, Hazekamp, et al., 2010) or even higher in modern chemovars are now encountered.

Many have argued that cannabis is primarily a botanical delivery device for THC, while others have espoused a more holistic assessment (see McPartland, Guy, & Di Marzo, 2014; Russo, 2011 for a broader discussion). Certainly, medical consumers must fall into the latter group, as sales figures for herbal cannabis overwhelm those for THC (Marinol®) as a pure compound. Sativex®, a standardized oromucosal whole cannabis extract that is now approved as a prescription in 29 countries, was purposely designed to incorporate terpenoids, which comprise 6%–7% of total cannabinoid (Guy & Stott, 2005).

While controlled double-blind trials exploring cannabinoid–terpenoid interactions have yet to take place and are sorely required, observational information has been offered: limonene added to THC enhanced the experience to be more "cerebral and euphoric," while myrcene rendered THC more "physical, mellow, sleepy." The three together were considered more "cannabimimetic" than THC alone (Name Withheld, 2006), THC taken in isolation being more dysphoric than euphoric (Calhoun et al., 1998), and displaying a much narrower therapeutic index than whole cannabis (Russo, 2011; Sellers et al., 2013). Clinical trial data comparing rates of adverse events also favor cannabis extracts over THC (Russo, 2013).

While the following will summarize prior publications, emphasis will be placed on newer findings and agents not previously examined in relation to cannabis pharmacology. Unless otherwise indicated, all the agents are Generally Recognized As Safe (GRAS) by the US Food and Drug Administration (FDA) and/or are approved as food additives by the Flavor and Extract Manufacturers' Association (FEMA). According to a recent publication (Giese, Lewis, Giese, & Smith, 2015), 50 cannabis terpenes are routinely encountered in North American chemovars, but 17 are most common, all of which are discussed herein. Of these, several predominate to form eight "Terpene Super Classes": myrcene, terpinolene, ocimene, limonene, α-pinene, humulene, linalool, and β-caryophyllene (BCP).

Similarly, Fischedick (2017) analyzed cannabis samples from a single California cannabis dispensary over the course of a year, and identified five terpenoid groups based on predominant content: myrcene, terpinolene, myrcene/limonene, caryophyllene, and bisabolol.

4. CANNABIS MONOTERPENOIDS (FIG. 3)

4.1 β-Myrcene

β-Myrcene is the most prevalent terpene in modern cannabis chemovars in the United States (Giese et al., 2015) and in Europe (Hazekamp, Tejkalová, & Papadimitriou, 2016), and is likely most responsible for

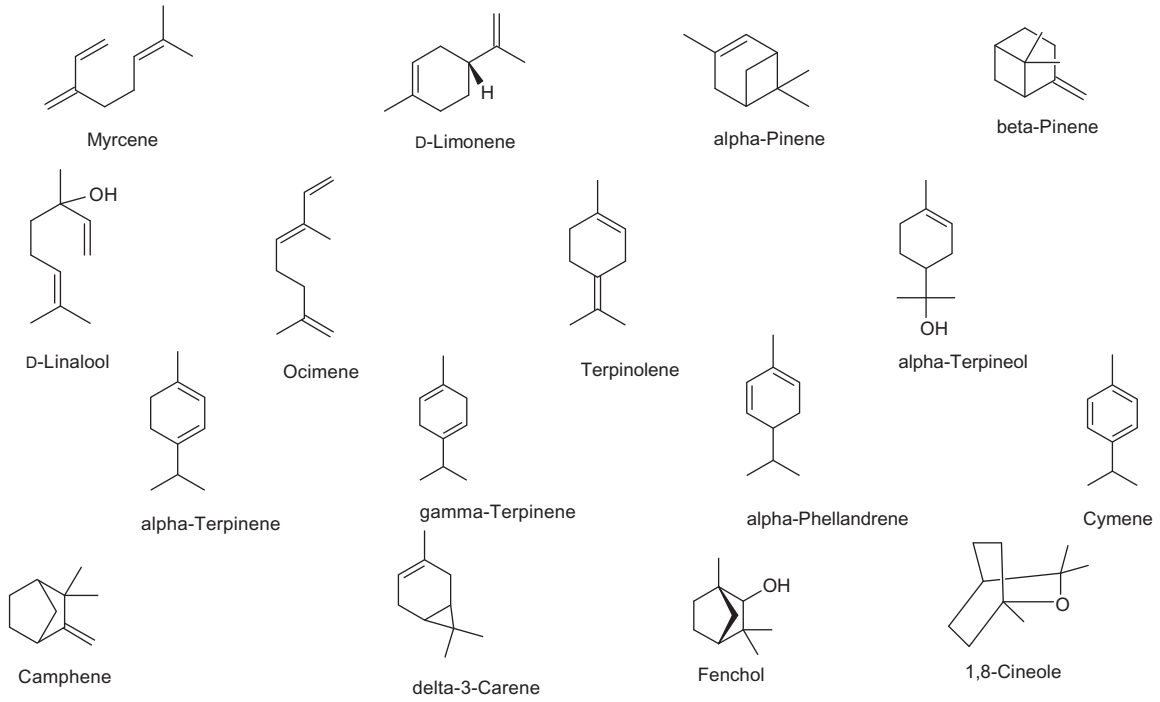


Fig. 3 Monoterpenoids commonly encountered in cannabis (all structures drawn by EBR using ChemSketch 2015.2.5).

sedative effects of many of the common preparations in commerce. As previously reviewed (Russo, 2011), myrcene is antiinflammatory via prostaglandin E-2 (PGE-2) (Lorenzetti, Souza, Sarti, Santos Filho, & Ferreira, 1991), blocks carcinogenic effects of aflatoxin in the liver (De-Oliveira, Ribeiro-Pinto, & Paumgartten, 1997), and is analgesic in mice, an activity that is abrogated by naloxone, the μ-opioid inverse agonist, suggesting a narcotic effect mediated by α-2 adrenoreceptors (Rao, Menezes, & Viana, 1990). This is less surprising recognizing that myrcene is one sedative agent of hops (*Humulus lupulus*) (Bisset & Wichtl, 2004). Additionally, it produces muscle relaxant effects in mice, and prolonged barbiturate sleep time (do Vale, Furtado, Santos, & Viana, 2002). These findings seem to explain the phenomenology of "couch-lock" commonly attributed to modern cannabis chemovars by its consumers.

More recent studies expand on these findings. In mice (Paula-Freire, Andersen, Gama, Molska, & Carlini, 2014), myrcene 10 mg/kg po (equivalent to 0.81 mg/kg in humans) (Reagan-Shaw, Nihal, & Ahmad, 2008) significantly increased paw lick latency in the hot-plate test, and reduced pain behavior in both phases of the formalin test. Interestingly, the duration of analgesic effect exceeds that of morphine (4 h) and once again, was abrogated by naloxone administration, supporting an opioid-related mechanism of action.

In human chondrocyte culture, myrcene inhibited NO production by IL-1β with an IC_{50} of 37.3 μg/mL, and at 50 μg/mL, lowered IL-1β-induced iNOS mRNA and protein by 78% (Rufino et al., 2015), suggesting therapeutic application in osteoarthritis.

In rats (Bonamin et al., 2014), oral myrcene 7.5 mg/kg (equivalent to 1.2 mg/kg in humans) demonstrated notable effects against peptic ulcers: decreased lesions in stomach and duodenum, increased mucus production, and mucosal malondialdehyde levels indicative of oxidative damage, decreased superoxide dismutase, but increased glutathione peroxidase, glutathione reductase, and total glutathione in the tissues. Similarly, in mice, myrcene 200 mg/kg ip (equivalent to 16.2 mg/kg in humans) for 10 days prevented ischemic/reperfusion oxidative injury via increases in glutathione, glutathione peroxidase, and superoxide dismutase, decreasing thiobarbituric acid reactive substances, and eliminating cerebral apoptosis and other histological changes (Ciftci, Oztanir, & Cetin, 2014). This activity suggests the possibility of synergistic benefits with the neuroprotective antioxidant effects of THC and CBD (Hampson et al., 1998; Lafuente et al., 2011).

4.2 D-Limonene

Limonene is a cyclic monoterpene common to citrus rinds and is common in nature, though more sporadically encountered in contemporary cannabis. It displays high bioavailability with 70% absorption after human pulmonary administration (Falk-Filipsson et al., 1993), is rapidly metabolized (Falk-Filipsson et al., 1993), but accumulates in adipose tissues and the brain, with an estimated human lethal dose of 0.5–5 g/kg. It is nonsensitizing (Von Burg, 1995).

Limonene is the parent compound to the entire family of monoterpenoids in the plant, and its biosynthetic enzyme, limonene synthase and others in cannabis are promiscuous in their substrates with various terpenoid end-products (Booth et al., 2017), via regulatory mechanisms that remain to be elucidated. Experiments in mice confirm limonene to be strongly anxiolytic, boosting serotonin levels in prefrontal cortex, and dopamine in hippocampus mediated via 5-HT_{1A} receptors (Carvalho-Freitas & Costa, 2002; Komiya, Takeuchi, & Harada, 2006; Pultrini Ade, Galindo, & Costa, 2006). Orange terpenes, primarily limonene, boosted mouse motility after inhalation by 35.25%, while decreasing activity after caffeine 33.19% (Buchbauer et al., 1993). Human clinical work supports these activities, as a study in Japan (Komori, Fujiwara, Tanida, Nomura, & Yokoyama, 1995), demonstrated that depressed patients exposed to citrus scent experienced normalization of Hamilton Depression Scores (HADS), allowing discontinuation of antidepressants in 9/12 hospitalized patients. Additionally, immune stimulation (CD4/8 ratio normalization) was documented. Limonene has an impressively supportive history as an "antidote" to excessive psychoactive adverse events produced by THC (Russo, 2011).

Limonene demonstrated prominent antibiotic effects vs *S. aureus* and *Pseudomonas aeruginosa* (Onawunmi, Yisak, & Ogunlana, 1984). Recently, concentrations of 400 μg/mL inhibited biofilm formation of the pathogen *Streptococcus pyogenes* SF370 and *S. nutans*, which produces dental caries, downregulating various genes mediating surface-associated proteins (Subramenium, Vijayakumar, & Pandian, 2015). Considering that cannabinoids also interfere with quorum-sensing in biofilm formation (Soni, Smoum, Breuer, Mechoulam, & Steinberg, 2015), cannabinoid/terpenoid synergy in this mechanism of action is certainly likely.

Citrus EOs were an effective treatment against dermatophytes (Sanguinetti et al., 2007; Singh et al., 2010), and display radical scavenging abilities (Choi, Song, Ukeda, & Sawamura, 2000). Two citrus EOs also suppressed *Propionibacterium acnes*, the pathogen in acne (MIC 0.31 μL/mL),

more powerfully than triclosan (Kim et al., 2008), while simultaneously lowering TNF-α production.

Limonene also demonstrates chemotherapeutic properties, inducing apoptosis of breast cancer cells among others. It was utilized in high doses in Phase II RCTs (Vigushin et al., 1998), with good safety, but less impressive efficacy. A more recent study in humans demonstrated that, in women with preoperative breast cancer, an oral intake of 2 g of D-limonene a day produced a mean concentration of 41.3 μg/g of biopsy breast tissue, and reduced cyclin D1 expression that could lead to cell-cycle arrest and decreased proliferation (Miller et al., 2013).

A blood orange (*Citrus sinensis*) volatile emulsion that was 95.35% D-limonene at 100 ppm induced apoptosis in Bcl-2 human colon cancer cells, activating p38 and inhibiting Akt, and inhibited the angiogenesis marker, vascular endothelial growth factor 80%, decreased cell migration, down-regulated MMP-9 expression, and reduced tube formation (Chidambara Murthy, Jayaprakasha, & Patil, 2012). Limonene's primary metabolite, perillic acid, also has cytotoxic effects, and additionally produces antianxiety effects in rat brain (Fukumoto et al., 2008).

A patent has been filed based on the ability of limonene to ameliorate gastro-esophageal reflux (Harris, 2010) and a commercial capsule preparation is available.

Limonene 10 mg/kg po reduced hyperalgesia in mice induced by intrathecal administration of HIV glycoprotein toxin gp120, as well as prevented increases in IL-1β and IL-10 levels (Piccinelli et al., 2017). Mechanical sensitivity induced by TNF-α, was prevented, as was IL-1β cold sensitivity.

Limonene 10 mg/kg po reduced inflammation scores, weight loss, and TNF-α in ibuprofen-induced rat colitis, as well as decreased peripheral IL-6 inflammatory marker in elderly humans receiving a daily supplement that was 95% limonene for 56 days (d'Alessio et al., 2013).

At high concentrations, limonene prevented oxidative damage in human lens epithelial cells via regulation of caspase-3 and -9, Bax, and Bcl-2, as well as inhibition of p38 MAPK phosphorylation (Bai, Zheng, Wang, & Liu, 2016), suggesting therapeutic use to prevent cataracts.

Limonene is an agonist at A_{2A} adenosine receptors (Park, Lee, Yaoyao, Jun, & Lee, 2011) and could synergize activity with both THC (direct activator) and CBD (uptake inhibitor via competition for the nucleotide binding site of the ENT1 transporter) (Carrier et al., 2006), a relationship that is now the subject of active research.

Limonene 50 μM increased mitochondrial biogenesis, activated the AMPK energy regulator, increased brown adipocyte markers PGC-1α

UCP1, and induced "browning" of 3T3-L1 adipocytes by activating β-3-AR and ERK signaling pathway (Lone & Yun, 2016), suggesting a putative role in obesity treatment. Certainly, interesting synergies are possible with the anorexic effects of CBD and THCV (McPartland et al., 2015), and modulatory effects of THC on weight and microbiome balance (Cluny, Keenan, Reimer, Le Foll, & Sharkey, 2015).

4.3 β-Ocimene

Ocimene is one of the most common monoterpenes found in nature. In the field of botanical medicine, there is an association of β-ocimene in EOs with anticonvulsant activity, antifungal activity, antitumor activity, and pest resistance (Bomfim et al., 2016; Cascone et al., 2015; Sayyah, Nadjafnia, & Kamalinejad, 2004). Ocimene is also a volatile pheromone important for the social regulation of honeybee colonies. The commercial applications of exploiting that attraction to produce "cannabis honey" have not been missed by the cannabis industry emerging in the United States, and subsequently by law enforcement agencies to detect illicit drugs by "trained honeybees," which were proposed to replace sniffer dogs in 2015 (Kennell, 2016; Maisonnasse, Lenoir, Beslay, Crauser, & Le Conte, 2010; Schott, Klein, & Vilcinskas, 2015).

Significant ocimene content is being reported by medical cannabis laboratories in California and Washington State (Elzinga et al., 2015). Ocimene is also a major component of the EO of cannabis varieties developed by the international medical cannabis producer, Bedrocan, which supplies standardized cannabis to pharmacies in Europe (Fischedick, Van Der Kooy, & Verpoorte, 2010). The effects and associations of cannabinoid and ocimene co-administration remain unclear but warrant further attention.

4.4 γ-Terpinene

This cyclic monoterpene is common to *Eucalyptus* spp., and to EO of cumin (*Cuminum cyminum*, 32%), whereas it is a minor component in cannabis. In mice, oral pretreatment with of 25–50 mg/kg (equivalent to 2–4 mg/kg human) inhibited extravasation of fluid in an acetic acid microvascular permeability model, reduced peritonitis after carageenan, neutrophil migration, and production of interleukin-1β and TNF-α vs controls, as well as lung inflammation after acute injury, thus demonstrating broad antiinflammatory effects (Ramalho, Pacheco de Oliveira, Lima, Bezerra-Santos, & Piuvezam, 2015). γ-Terpinene demonstrated little antioxidant or antiproliferative activity in a recent experiment (Fitsiou et al., 2016).

4.5 α-Terpinene

A major component of tea tree oil (*Melaleuca alternifolia*, 13%) it is found in low concentrations in cannabis. It inhibited oxidation of LDL and linoleic acid and was potent as a scavenger of DPPH radicals (Tisserand & Young, 2014). It demonstrated modest activity as a synergist to diminazene aceturate in treatment of *Trypanasoma evansi*, a protozoal pathogen of horses and other animals (Baldissera et al., 2016).

4.6 α-Terpineol

Terpineol is a cyclic monoterpenoid alcohol (Bhatia, Letizia, & Api, 2008). Its inhalation diminished mouse motility 45% (Buchbauer et al., 1993). It displayed dose-dependent antibiotic efficacy vs *S. aureus*, *S. epidermidis*, and *P. acnes* (Raman, Weir, & Bloomfield, 1995), among others, particularly in its customary vehicle of tea tree oil (*M. alternifolia*) (Carson & Riley, 1995). An MIC of 0.78 μL/mL was noted on *Escherichia coli*, with observed cell wall and membrane rupture (Li et al., 2014). α-Terpineol 100 μg/disk produced significant zones of inhibition in culture of four drug-resistant *Helicobacter pylori* cultures (Miyamoto, Okimoto, & Kuwano, 2014). Moderate effects against two strains of *Plasmodium falciparum* malaria were noted in an EO with major terpineol component (Campbell, Gammon, Smith, Abrahams, & Purves, 1997).

The small cell lung cancer cell line NCI-H69 was sensitive to α-terpineol at a high dose (IC_{50} approximately 260 μM) via suppression of NF-κB signaling (Hassan, Gali-Muhtasib, Goransson, & Larsson, 2010). In a U937 leukemia cell line, α-terpineol reduced LPS-induced cytokine production of IL-1β, IL-6, and IL-10, but not TNF-α (Nogueira, Aquino, Rossa Junior, & Spolidorio, 2014).

Nociceptive behavior in mice was significantly reduced by doses of 25 mg/kg ip and above on early and late paw licking post formalin, writhing after ip acetic acid, and after paw injections of glutamate or capsaicin, without motor impairment (Quintans-Junior et al., 2011). Similarly, 50–100 mg/kg ip dosing in mice inhibited hyperalgesia postcarageenan or TNF-α, PGE2, or DA administration, and neutrophil migration in a pleurisy model (de Oliveira et al., 2012).

It was reported that fatty liver was produced in mice after daily injections of 10 or 500 mg/kg ip of α-terpineol for 2 weeks (Choi, Sim, Choi, Lee, & Lee, 2013), an exposure level likely never attainable with a cannabis-based medicine.

Two recent studies from Iran are of interest. Pretreatment with α-terpineol 5–20 mg/kg ip significantly reduced jumping behavior typical

of withdrawal effect in mice rendered morphine-dependent (Parvardeh, Moghimi, Eslami, & Masoudi, 2016), while 20–40 mg/kg ip doses reduced the development of tolerance to morphine analgesia. These results suggest possible synergy of this ingredient with other cannabis components attenuating addiction: CBD and BCP (Russo, 2011).

Higher doses of α-terpineol (50–200 mg/kg ip) in rats subjected to cerebral ischemia improved spatial learning in a water maze vs controls, restored hippocampal long-term potentiation, and lowered malondialdehyde levels indicative of lipid peroxidation (Moghimi, Parvardeh, Zanjani, & Ghafghazi, 2016). This activity certainly suggests the possibility of synergistic benefit in conjunction with benefits ascribed to CBD in similar experiments in newborn pigs (Lafuente et al., 2011).

4.7 α-Pinene

α-Pinene, a bicyclic monoterpene, is the most widely distributed terpenoid in Nature (Noma & Asakawa, 2010), but this versatile therapeutic agent is unfortunately represented in lower concentration in modern cannabis chemovars, although it is reportedly relatively abundant in the "Blue Dream" chemovar in Southern California (Backes, 2014). It has high bioavailability via inhalation (60%) with rapid metabolism and redistribution (Falk et al., 1990).

Its pharmacological effects are legion: antiinflammatory via PGE-1 (Gil, Jimenez, Ocete, Zarzuelo, & Cabo, 1989), bronchodilator in humans at low exposure levels (Falk et al., 1990), antibiotic in EO that was equally effective as vancomycin against MRSA and other resistant bacteria (Kose, Deniz, Sarikurkcu, Aktas, & Yavuz, 2010) (MIC 125 μg/mL) in an EO of *Salvia rosifolia* composed of 34.8% pinene, and was the most potent compound in a tea tree EO vs *P. acnes* and *Staph* spp. (Raman et al., 1995). Efficacy was also noted for α-pinene for MRSA, *Cryptococcus neoformans* and *Candida albicans* biofilms (Rivas da Silva et al., 2012). α-Pinene dramatically increased antibiotic efficacy by lowering the MIC of ciprofloxacin, erythromycin, and triclosan against the gastroenteritis pathogen, *Campylobacter jejuni*, by promoting *cmeABC* and *Cj1687* antimicrobial efflux genes, decreasing bacterial membrane integrity, and disrupting heat-shock responses (Kovac et al., 2015). It was also beneficial against *Leishmania amazonensis* promastigotes (IC_{50} 19.7 μg/mL) and axenic and intracellular amastigote forms (IC_{50} 43.9 and 38.1 μg/mL) (Rodrigues et al., 2015). α-Pinene demonstrated larvicidal activity against *Anopholes subpictus*, vector of malaria (LC_{50} [lethal concentration] 32.09 μg/mL), *Aedes albopictus*, vector of dengue (LC_{50} 34.09 μg/mL), and

Culex tritaeniorhynchus, vector of Japanese encephalitis (LC_{50} 36.75 μg/mL) (Govindarajan, Rajeswary, Hoti, Bhattacharyya, & Benelli, 2016).

Pinene increased mouse motility after inhalation 13.77% (Buchbauer et al., 1993). Its greatest therapeutic value may derive from its acetylcholinesterase inhibition (Perry, Houghton, Theobald, Jenner, & Perry, 2000), producing an IC_{50} of 0.44 mM (Miyazawa & Yamafuji, 2005), which serves to reduce or eliminate one of the primary adverse events associated with THC, that of short-term memory impairment. This ability may also serve admirably in treatment of dementia, a syndrome in which THC has already produced benefits in counteracting agitation (Russo, Guy, & Robson, 2007; Volicer, Stelly, Morris, McLaughlin, & Volicer, 1997).

Inhalation of α-pinene in mice at 10 μL/L concentration produced an anxiolytic effect in the elevated plus maze, with general brain distribution and increase in tyrosine hydroxylase mRNA in the midbrain (Kasuya et al., 2015). In chronic inhalation over 5 days, anxiolytic effects were maintained (Satou, Kasuya, Maeda, & Koike, 2014).

α-Pinene has also been suggested as a modulator of THC overdose events (Russo, 2011), with historical anecdotes supporting its use as an antidote to cannabis intoxication. α-Pinene at a concentration of 2 μg/mL produced 69% protection in rat astrocytes against H_2O_2-induced cell death (Elmann et al., 2009).

Chronic pinene exposure led to decreased melanoma growth in mice at 180 ng/L (1 ppm) in ambient air, a dose too low to directly affect tumor (Kusuhara et al., 2012). This mental health-promoting effect attributed here to pinene exposure, is known in Japan as "Shinrin-yoku" or "forest bathing." In contrast, a direct synergistic and isobolographic benefit was observed with α-pinene in combination with paclitaxel vs nonsmall-cell A549 lung carcinoma cells with evidence of apoptosis (Zhang et al., 2015). α-Pinene inhibited BEL-7402 human hepatoma cell growth 79.3%, both time and dose dependently over 3 days at 8 mg/L concentration (Chen et al., 2015), causing cycle arrest in G2/M phase, a decrease in tumor xenografts vs control ($P < 0.01$), and equivalent to that from 5-flurouracil, an increase in Chk1 and -2 expression, indicative of DNA damage leading to cell death.

4.8 β-Pinene

A bicyclic monoterpene isomer, β-pinene is commonly encountered in conjunction with α-pinene. It proved to have equal antibiotic efficacy to α-pinene against *S. aureus* (MRSA), and *C. neoformans* and *C. albicans* biofilms (Rivas da Silva et al., 2012). Like its isomer, β-pinene demonstrated the ability to synergize with paclitaxel vs nonsmall-cell A549 lung carcinoma

cells with evidence of apoptosis (Zhang et al., 2015), but unlike α-pinene, it failed to prevent astrocyte damage by H_2O_2 (Elmann et al., 2009). Little additional pharmacological research has been evident otherwise on the pure compound, particularly with regard to its psychopharmacology.

4.9 Linalool

Linalool is a noncyclic monoterpenoid that is commonly extracted from lavender (*Lavandula* spp.), rose (Rosa spp.), basil (*Ocimum basilicum*), and neroli oil (*Citrus aurantium*). The psychotropic anxiolytic activity has been reviewed in detail (Russo, 2001, 2011). Linalool has established sedative, antidepressant, anxiolytic, and immune potentiating effects and can represent a significant portion (<6%) of the EO of cannabis (McPartland & Russo, 2001). This terpene can also have analgesic and anticonvulsant effects (Batista et al., 2010; Leal-Cardoso et al., 2010; Peana et al., 2006; Russo, 2011). It is also antinociceptive at high doses in mice via ionotropic glutamate receptors (Batista et al., 2008). Linalool demonstrated anticonvulsant and antiglutamatergic activity, and reduced seizures as part of *O. basilicum* EO after exposure to pentylenetetrazole, picrotoxin, and strychnine (Elisabetsky, Marschner, & Souza, 1995; Ismail, 2006). Furthermore, linalool decreased K^+-stimulated glutamate release and uptake in mouse synaptosomes (Silva Brum, Emanuelli, Souza, & Elisabetsky, 2001). Recent reports support the possibility that small concentrations found in certain cannabis chemovars may exert anticonvulsant benefits in human patients (Russo, 2016b; Sulak, Saneto, & Goldstein, 2017).

Linalool alone demonstrated an MIC of 0.625 μL/mL on *P. acnes* (Kim et al., 2008). Linalool in ambient air decreased mouse motility 73%, confirming its potent sedative effects (Buchbauer et al., 1993). In traditional aromatherapy, linalool is the likely suspect in the remarkable therapeutic capabilities of lavender EO to alleviate skin burns without scarring (Gattefosse, 1993). Pertinent to this, the local anesthetic effects of linalool are equal to those of procaine and menthol (Ghelardini, Galeotti, Salvatore, & Mazzanti, 1999; Re et al., 2000). Another explanation would be its ability to produce hot-plate analgesia in mice ($P<0.001$) that was reduced by administration of an adenosine A_{2A} antagonist (Peana et al., 2006). This terpene can also influence CYP enzymes in rat liver, suggesting that it can alter the pharmacokinetics of cannabis administration (Noskova, Dovrtelova, Zendulka, Řemínek, & Jurica, 2016).

Linalool displays powerful antileishmanial activity, and as a presumed lavender EO component, decreased morphine opioid usage after inhalation

vs placebo ($P=0.04$) in gastric banding in morbidly obese surgical patients (do Socorro et al., 2003; Kim et al., 2007). Linalool incorporated nanoparticles are being explored as a novel anticancer agent (Han et al., 2016).

4.10 Camphene

Camphene is a cyclic monoterpene common to conifers, especially Douglas fir (*Pseudotsuga menziesii*), and is present in many cannabis chemovars in low titer. In an ointment with menthol and other EOs, camphene reduced experimentally induced bronchospasm in animals, suggesting application in human chronic obstructive pulmonary disease (Schafer & Schafer, 1981).

Camphene administered to hyperlipidemic rats at 30 μg/g (equivalent to 4.87 mg/kg in humans) led to a 54.5% decrease in total cholesterol, 54% in LDL-cholesterol, and 34.5% in triglycerides (all $P<0.001$) (Vallianou, Peroulis, Pantazis, & Hadzopoulou-Cladaras, 2011). Reductions in cholesterol in HepG2 cells paralleled those attained with mevinolin, but in contrast, camphene seemingly worked independently of HMG-CoA reductase inhibition. Synergy of camphene with other components of Chios mastic gum (*Pistacia lentiscus*) was also observed. In subsequent work (Vallianou & Hadzopoulou-Cladaras, 2016), camphene inhibited cholesterol production 39% at 100 μM in HepG2 cells, while also decreasing triglycerides 34% and increasing apolipoprotein AI expression, likely mediated via SREBP-1 upregulation and MTP inhibition.

Camphene displayed weak antinociceptive effects on acetic acid-induced writhing in mice at 200 mg/kg (Quintans-Junior et al., 2013), but prevented AAPH-induced lipoperoxidation at 0.01 μg/mL, and demonstrated antioxidant activity and superoxide radical inhibition at the same concentration.

Camphene supplemented to the high-fat diet of mice at the high dose of 200 mg/kg/day (corresponding to 16 mg/kg/day in humans) reduced 17% body weight reduction vs controls (Kim, Choi, Choi, Choi, & Park, 2014), and increased adiponectin levels and receptor mRNA expression in liver.

Camphene induced apoptosis in a variety of cancer cell lines, notably B16F10-Nex2 melanoma with an IC_{50} of 71.2 μg/mL (Girola et al., 2015) and produced chromatin condensation, shrinkage of cells, apoptotic body formation, fragmentation of nucleus and activation of caspase-3. It was also active against grafted tumor with peritumoral injection (10 mg/mL) in mice.

Camphene was utilized as a porogen for the production of nano/macroporous polycaprolactone microspheres for injectable cell delivery (Kim, Hwang, & Shin, 2016).

4.11 Terpinolene

Terpinolene is a cyclic monoterpene, common to *Pinus* spp., but richest in parsnip EO (*Pastinaca sativa* 69%) (Tisserand & Young, 2014). It is a common component of some commercial cannabis chemovars (Giese et al., 2015), its presence is said to be characteristic of "sativa" types (Hazekamp et al., 2016).

Terpinolene has been demonstrated to prevent LDL oxidation, of interest in treatment of atherogenesis and coronary artery disease (Grassmann, Hippeli, Spitzenberger, & Elstner, 2005).

It was sedative in mice at 0.1 mg, reducing motor activity to 67.8% (Ito & Ito, 2013), whereas subjective reports in humans suggest greater stimulation in terpinolene-rich cannabis chemovars (data on file, Napro Research 2016), possibly attributable to cholinesterase inhibition effects in the presence of THC, a pharmacological effect measured with IC_{50} at 156.4 μg/mL (Bonesi et al., 2010).

At a concentration of 0.05%, terpinolene markedly reduced AKT1 expression in K562 human CML cells and significantly stimulated apoptosis (Okumura, Yoshida, Nishimura, Kitagishi, & Matsuda, 2012). At extreme dosing (>50 mg/L), terpinolene demonstrated marginally greater antiproliferative effects against neuroblastoma as compared to neuronal cell lines (Aydin, Turkez, & Tasdemir, 2013). Over a similar dosage range, it showed antioxidant effects in human lymphocytes (Turkez, Aydin, Geyikoglu, & Cetin, 2015).

Terpinolene is reportedly also antifungal and larvicidal (Aydin et al., 2013). A subactive antinociceptive and antiinflammatory dosage of 3.125 mg/kg po in rats synergized with diclofenac, and reduced hyperalgesia, an effect blocked by ketanserin, suggesting mediation via 5-HT_{2A} receptors (Macedo et al., 2016).

4.12 α-Phellandrene

A cyclic monoterpene, α-phellandrene is widespread in nature, but rich in frankincense (*Boswellia sacra*), comprising 42% of the EO (Tisserand & Young, 2014). It produced cholinesterase inhibition with an IC_{50} of 120.2 μg/mL (Bonesi et al., 2010). Multiple assays in mice (Lima et al., 2012) demonstrated antinociceptive effects: acetic acid-induced abdominal

writhing (3.125 mg/kg/po or 0.25 mg/kg human equivalent), both phases of the formalin test (50 mg/kg/po, or 0.54 mg/kg human), capsaicin injection (3.125 mg/kg/po, or 0.25 mg/kg human equivalent), glutamate injection (12.5 mg/kg/po, or 1 mg/kg human) and carageenan injection (only at 3 h at 25 mg/kg/po, or 2 mg/kg human). Effects were blocked by multiple agents, suggesting mediation by glutamatergic, opioid, nitrergic, cholinergic, and adrenergic mechanisms.

In rats, phellandrene at 10 mg/kg/d po (1.6 mg/kg human equivalent) prevented spared nerve injury-induced mechanical and cold hyperalgesia, while also demonstrating an antidepressant effect in reducing immobility in the forced swim test 85%, but without decreasing locomotor activity in the open field (Piccinelli et al., 2015).

While not demonstrating antimicrobial effects per se, phellandrene mildly stimulated macrophage proliferation in mice via Mac-3 and promoted function in vivo (Lin et al., 2013), suggesting ability to suppress intracellular bacterial growth.

Subsequent work demonstrated a wide variety of effects on gene expression affecting DNA repair, cell cycle, and apoptosis in WEHI-3 murine leukemia cells (Lin et al., 2015, 2014).

At 30 μM concentration with 24 h of exposure, 15.8% of human liver tumor J5 cells became necrotic, possibly due to depletion of ATP (Hsieh et al., 2014). Subsequently, findings were attributed to multiple pathways: regulation of mTOR, LC-3II expression, p53 signaling and NF-κB activation (Hsieh et al., 2015).

In carageenan injections in rodents, phellandrene 50 mg/kg po pretreatment induced neutrophil migration inhibition, and TNF-α release (both $P<0.001$) (Siqueira et al., 2016) and decreased mast cell degranulation ($P<0.05$), suggesting possible applications in arthritic and allergic conditions.

4.13 γ-Cadinene

A bicyclic sesquiterpene, while more common in other EOs, it is found at low concentration in current cannabis chemovars tested (Hazekamp et al., 2016). Cadinene demonstrated larvicidal activity against *Anopholes stephensi*, vector of malaria (LC_{50} [lethal concentration] 8.23 μg/mL), *Aedes aegypti*, vector of dengue (LC_{50} 9.03 μg/mL), and *Culex quinquefaciatus*, vector of filariasis (LC_{50} 9.86 μg/mL) (Govindarajan, Rajeswary, & Benelli, 2016). Little additional pharmacological data is available on the isolated compound.

4.14 Δ^3-Carene

A bicyclic monoterpenoid alkene most associated with turpentine from conifers, it is also prevalent in white pepper (*Piper nigrum*, 25%) (Tisserand & Young, 2014), but is found in low concentration in cannabis.

Studies from Scandinavia in sawmills have documented high-exposure human irritancy reactions in skin and lungs, with pulmonary intake and slight increased airway resistance at 450 mg/m^3 exposure (Falk et al., 1991), with rapid metabolism and high adipose tissue affinity. The occupational exposure limit recommendation in Sweden for it or other turpentine components is 150 mg/m^3 (Kasanen et al., 1999). Carene hydroperoxide was noted to be an allergen (Edman et al., 2003), and skin sensitization in guinea pigs at very high concentrations increased airway reactivity (Lastbom, Boman, Johnsson, Camner, & Ryrfeldt, 2003). Carene concentrations, along with limonene and pinene, are common volatile organic compounds elevated in new home construction (Krol, Namiesnik, & Zabiegala, 2014).

Carene was rapidly absorbed, distributed, and metabolized in human volunteers after oral administration (Schmidt, Belov, & Goen, 2015). A low concentration (5 μM) stimulated mineralization in mouse osteoblastic cells by increasing protein expression; activation of MAP kinases; and expression of osteoblast genes, osteopontin, and type I collagen (Jeong, Kim, Min, & Kim, 2008), suggesting a possible therapeutic role in osteoporosis treatment.

Carene demonstrated larvicidal activity against *Anopholes stephensi*, vector of malaria (LC_{50} [lethal concentration] 16.37 μg/mL), *A. aegypti*, vector of dengue (LC_{50} 17.91 μg/mL), and *C. quinquefaciatus*, vector of filariasis (LC_{50} 19.5 μg/mL) (Govindarajan, Rajeswary, Hoti, et al., 2016; Govindarajan, Rajeswary, et al., 2016).

Carene content was judged to be a marker of "sativa" cannabis chemovars (Hazekamp et al., 2016).

4.15 ρ-Cymene

A cyclic monoterpene, common to thyme (*Thymus vulgaris*) (27.4%), but a minor component in cannabis, ρ-cymene was active against *Bacteroides fragilis*, *C. albicans*, and *Clostridium perfringens* (Carson & Riley, 1995). It was sedative in mice at 0.04 mg in air, reducing motor activity to 47.3% of baseline (Ito & Ito, 2013). Additionally, it statistically significantly reduced acetic acid-induced writhing and both phases of formalin-induced pain in mice at 50 mg/kg (Quintans-Junior et al., 2013). It showed little antioxidant or antiproliferative effects in a recent study (Fitsiou et al., 2016).

4.16 Fenchol

A bicyclic monoterpenoid, fenchol (or fenchyl alcohol) is an FDA-approved flavor additive and rated GRAS by FEMA (Bhatia, McGinty, Letizia, & Api, 2008). Oral doses above 2 g/kg were fatal in rats, demonstrating lethargy, ataxia, flaccidity, and coma, whereas a 4% cutaneous application in humans was nonsensitizing. It is common to basil (*O. basilicum*), and to California cannabis chemovars (Giese et al., 2015), but in low concentrations, such that the noted toxicity would be unlikely a factor even in concentrates.

4.17 1,8-Cineole (Eucalyptol)

This bicyclic monoterpenoid ether is a major component of *Eucalyptus* spp. EOs, and is largely responsible for their pharmacology (Barbosa, Filomeno, & Teixeira, 2016). A prior review (McPartland & Russo, 2001) noted its myriad activities including increasing cerebral blood flow after inhalation, increasing rat locomotion, and as an antiinflammatory, analgesic, antibiotic, antifungal, and antiviral against *Herpes simplex 2*, but it is barely present in modern cannabis chemovars (Hazekamp et al., 2016).

5. CANNABIS SESQUITERPENOIDS (FIG. 4)

5.1 β-Caryophyllene

BCP, a bicyclic sesquiterpenes alkene, is the most common terpenoid in cannabis extracts, and is nearly ubiquitous in food in the food supply. The extensive potent and various pharmacological activities for BCP summarized below, are rarely noted for any individual compound that also has a wide therapeutic index, safety, and low toxicity. BCP acts as a selective full agonist at CB_2 with strong potency (100 nM), and its antiinflammatory effects are reduced in CB_2 knockout mice (Gertsch, 2008). BCP activity at CB_2 has been confirmed in rodent models of nociception and pain (Katsuyama et al., 2013; Paula-Freire et al., 2014), colitis (Bento et al., 2011), and nephrotoxicity (Horváth, Mukhopadhyay, Haskó, & Pacher, 2012). Russo (2011) proposes mechanisms whereby BCP synergizes with THC to impart antipruritic effects and gastric cytoprotection, and with CBD to impart antiinflammatory benefits. CB_2 agonists (likely including caryophyllene) have been shown to reduce drug administration (cocaine) and improve scores of depression and anxiety in animal models (Bahi et al., 2014; Onaivi et al., 2008; Xi et al., 2011). BCP demonstrated larvicidal activity against *A. subpictus*, vector of malaria (LC_{50} [lethal concentration]

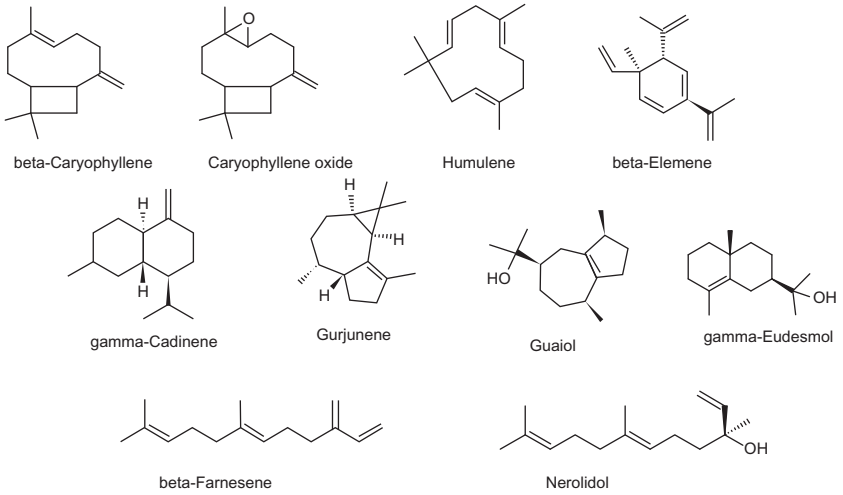


Fig. 4 Sesquiterpenoids commonly encountered in cannabis (all structures drawn by EBR using ChemSketch 2015.2.5).

41.66 μg/mL), *A. albopictus*, vector of dengue (LC_{50} 44.77 μg/mL), and *C. tritaeniorhynchus*, vector of Japanese encephalitis (LC_{50} 48.17 μg/mL) (Govindarajan, Rajeswary, Hoti, et al., 2016; Govindarajan, Rajeswary, et al., 2016). As a monotherapeutic agent, BCP provides many other benefits, reviewed by Fidyt, Fiedorowicz, and Strządała (2016).

According to an exhaustive review, BCP activates peroxisome proliferated activator receptors (PPARs) isoforms, inhibits pathways triggered by the activation of toll-like receptor complexes (i.e., CD14/TLR4/MD2), reduces immunoinflammatory processes, and exhibits synergy with μ-opioid receptor pathways (Sharma et al., 2016). Additionally, BCP is a potent antagonist of homomeric nicotinic acetylcholine receptors (7-nAChRs) and devoid of effects mediated by serotonergic and GABAergic receptors. BCP modulates numerous molecular targets by altering their gene expression, signaling pathways, or through direct interaction. Basic experiments have demonstrated strong evidence for cardioprotective, hepatoprotective, gastroprotective, neuroprotective, nephroprotective, antioxidant, antiinflammatory, antimicrobial, and immunemodulator activities. Thus, it has shown potent therapeutic promise in neuropathic pain, neurodegenerative, and metabolic diseases. A recent publication extends its therapeutic potential to protection from alcoholic steatohepatitis via antiinflammatory effects and alleviation of metabolic disturbances (Varga et al., 2017).

The concentration of this important cannabis component was reduced to 10% by gamma-irradiation, a technique undertaken to eliminate bacterial contaminants (Hazekamp et al., 2016).

5.2 Caryophyllene Oxide

Caryophyllene oxide is a sesquiterpenoid oxide common to lemon balm (*Melissa officinalis*), and to the eucalyptus, *Melaleuca stypheloides*, whose EO contains 43.8% (Farag et al., 2004). Caryophyllene oxide is nontoxic and nonsensitizing, and has the distinction of being the component responsible for cannabis identification by drug-sniffing dogs (Opdyke, 1983; Stahl & Kunde, 1973). This compound serves as a broad-spectrum antifungal in plant defense and as an insecticidal/antifeedant (Bettarini et al., 1993; Langenheim, 1994). Therapeutic applications of caryophyllene oxide could exploit the antifungal efficacy observed in clinical study of onychomycosis compared to ciclopiroxalamine and sulconazole, with an 8% concentration affecting eradication in 15 days (Yang, Michel, Chaumont, & Millet-Clerc, 1999). This agent also demonstrates antiplatelet aggregation properties in vitro (Lin et al., 2003).

5.3 Humulene (α-Caryophyllene)

Humulene provides some defense to plants and their products, as this compound can inhibit fruit fly mating (Shelly & Nishimoto, 2015). Humulene at a concentration of 1.5 μg/mL produced 50% protection in rat astrocytes against H_2O_2-induced cell death, and was concentrated seven-fold in those cells (Elmann et al., 2009). The potentiating effect of BCP on the anticancer activity of α-humulene, isocaryophyllene, and paclitaxel against MCF-7, DLD-1, and L-929 human tumor cell lines has been evaluated (Legault & Pichette, 2007). A noncytotoxic concentration of BCP significantly increased the anticancer activity of α-humulene and isocaryophyllene on MCF-7 cells: α-humulene or isocaryophyllene alone (32 μg/mL) inhibited cell growth by about 50% and 69%, respectively, compared with 75% and 90% when combined with 10 μg/mL BCP. Little additional pharmacology, particularly psychopharmacology of the compound has been evident; a recent major review of *H. lupulus* (hops), of which it is a major EO component, merely mentioned its presence without additional commentary (Zanoli & Zavatti, 2008).

5.4 β-Elemene

Elemene is a monocyclic sesquiterpenoid polyalkene reported from some cannabis chemovars, and common to myrrh (*Commiphora myrrha*, 9%) and other similar resins (Tisserand & Young, 2014). Elemene via injection has been approved by the regulatory authority in China since 1993 for treatment of cancer. However, a 2006 Cochrane-style review or 127 RCTs showed poor adherence to CONSORT recommendations and very low Jadad scale scoring in available studies (Peng et al., 2006). A subsequent study in rats at 80 mg/kg IV (equivalent to 13 mg/kg in humans) showed good passage through the blood–brain barrier and attainment of high brain tissue levels, as well as noteworthy tumor inhibition and life extension (Wu et al., 2009). A more recent meta-analysis of studies in malignancy (Xu, Zheng, Li, Xu, & Fu, 2013) examined clinical studies up to 2011, examining claims of efficacy in 38 relevant trials. Overall response rate of elemene with chemotherapy was favorable in lung cancer ($P < 0.00001$), hepatic carcinoma ($P = 0.002$), metastatic brain cancer ($P = 0.02$), and leukemia ($P = 0.0004$), but not in gastric carcinoma. Clinical benefit was also seen in combination therapy vs chemotherapy alone in 13 lung cancer trials, 5 with hepatic carcinoma, 7 with gastric carcinoma, and 5 with leukemia, out of 30 examined. Similar comparison failed to show improved 1-year survival in lung cancer or liver cancer, or 2-year survival in lung cancer. Higher degrees of leukopenia were significantly lower ($P = 0.0007$) in the elemene plus chemotherapy groups.

Various subsequent studies have examined mechanisms of action of elemene in malignancy. Elemene 100 μM increased cytotoxicity significantly in various cell lines overexpressing the ABCB1 transporter of paclitaxel, colchicine, and vinblastine by inhibiting it efflux activity. Elemene significantly diminished mRNA transcription and P-gp and BCRP gene expression, as well as CD44 and 24-/low cell and $CBRP^{+}$ cell rates and serum-free cell sphere forming in breast cancer stem cells (Dong et al., 2015). It also dose dependently inhibited survival and proliferation of glioblastoma multiforme cell lines when combined with temozolomide or radiation (Liu et al., 2015) by inhibiting DNA repair via effects on ATM, AKT, and ERK signaling. In A549 human basal cells, elemene increased radiosensitivity through upregulation of p53 and downregulation of Bcl-2-producing apoptosis, and downregulation of DNA-PKcs inhibiting DSB repair (K. Zou, Liu, Zhang, & Zou, 2015). Radiosensitivity of gastric cancer was also enhanced by diminished Pak1 activation (Liu et al., 2015). Elemene was the first drug reported to inhibit TOPO I and IIα simultaneously, as demonstrated in

HepG-2 human hepatic carcinoma, producing cell arrest in S phase and apoptosis (Gong et al., 2015). Elemene mediated multidrug resistance or various genes in exosomes in MCF-7 human breast cancer cells, sensitizing them to docetaxel and adriacin (Zhang et al., 2015). In ECA-109 esophageal carcinoma cells, elemene reduced proliferation significantly via regulation of inhibition of hTERT expression by IncRNA CDKN2B-AS1 (Hu et al., 2015). In U87 glioblastoma cells, elemene reduced proliferation, increase apoptosis, reduced invasiveness, and mouse xenograft growth (Zhu et al., 2015), while downregulating stemness markers CD133 and ATP-binding cassette subfamily G member 2 and N-cadherin and β-catenin mesenchymal markers. In a review of molecular mechanisms (Jiang et al., 2016), elemene was noted to inhibit cancer growth via multiple mechanisms of proliferative signaling suppression: MAPK and PI3K/Akt/mTOR pathways, upregulation of growth suppressors, promotion of apoptosis, diminishing invasion and metastasis, affecting cell immortality, and reducing angiogenesis. While concentrations of elemene employed would likely never be attained with cannabis extracts, the distinct possibility of synergy or elemene with chemotherapeutic phytocannabinoids should certainly be explored. Combination with THC, CBD (Marcu et al., 2010), and temozolomide (Torres et al., 2011) for treatment of glioblastoma multiforme would be especially worthy of investigation.

A 0.5% elemene emulsion injection proved effective as a sclerosing agent in 23 consecutive patients treated for chylothorax with good reported safety (Jianjun, Song, Yin, Jia, & Donglei, 2008).

Elemene prevented human umbilical vein endothelial cell (HUVEC) damage by hydrogen peroxide in vitro, inhibited smooth muscle proliferation and migration, and neointima formation after vessel injury in rats (Wu, Wang, Tang, Long, & Yin, 2011). In subsequent work (Liu et al., 2015), elemene also decreased reactive oxygen species (ROS) and mitogen-activated protein kinase signaling in HUVECs, and suggesting utility in atherosclerosis treatment.

In a rat model of hepatic fibrosis, elemene downregulated plasma endotoxins, serum TNF-α, and expression of CD14, the coreceptor for bacterial lipopolysaccharide detection (Liu et al., 2011).

Elemene 12.5–50 μg/mL inhibited osteogenic differentiation from cultured human hip joint capsule fibroblasts via inhibition of the BMP/SMADs pathway, suggesting its ability to reduce ectopic ossification in ankylosing spondylitis (Zhou et al., 2015).

Elemene 10–200 μg/mL also reduced viability and increased apoptosis of rheumatoid arthritis fibroblast-like synoviocytes via induction of ROS and p38 MAPK activation, implying therapeutic potential in that disorder (Zou et al., 2016).

Elemene presence was said to be characteristic of "indica" chemovars of cannabis (Hazekamp et al., 2016). Although its concentrations in most cannabis chemovars are low, emphasis is placed here due to its versatility as a potential anticancer agent worthy of selective breeding to increase its titer, and possibly synergize with chemotherapeutic phytocannabinoids (Ligresti et al., 2006).

5.5 Guaiol

According to Lawless (1995), guaiol, a bicyclic sesquiterpenoid alkene alcohol, is a major component (42%–72%) of the EO of guaiacwood from the species *Bulnesia sarmienti*, a tree of Paraguay and Argentina, with a pleasant rose-like aroma, and is nontoxic, nonirritating, and nonsensitizing. It has been employed in aromatherapy to treat arthritis, rheumatoid arthritis, and gout. Reported actions of the EO are antiinflammatory, antioxidant, antirheumatic, antiseptic, diaphoretic, diuretic, and laxative. The EO of another species in which guaiol was a component displayed antibiotic properties (de Moura et al., 2002). A report (Parker, 2003) has also shown guaiol to have weak 5-alpha reductase inhibitory effects, and this could be helpful in benign prostatic hyperplasia, or even in treatment of male-pattern baldness, a benefit of cannabis reported independently in the Arabic and Chinese literature.

Guaiol inhibited nonsmall-cell lung cancer cells in vitro, and in vivo in nude mice (as effectively as cisplatin at the same 8 mg/kg dose) (Yang et al., 2016) with mitotic arrest in S phase in A549 and H1299 cells, downregulation of RAD51 homologous recombination repair factor and inducing apoptosis.

Guaiol showed contact toxicity for two moth species and efficacy as a fumigant for *Musca domestica* houseflies with LC_{50} of 16.9 μL/L (Liu, Wang, Xie, & Mu, 2013). It also demonstrated bite-deterrence index (BDI) against *A. aegypti* of 0.82, and vs *Anopholes quadrimaculatus* a BDI of 0.82, comparable to *N,N*-dimethyl-toluamide (DEET) at a concentration of 25 nM/cm^3, but was ineffective against larvae (Ali et al., 2015).

Guaiol was said to be a distinguishing factor in Afghan cannabis chemovars (Hillig & Mahlberg, 2004), with similar claim for "indica" chemovars (Hazekamp et al., 2016). As a sesquiterpenoid alcohol, it would be expected to produce sedative effects (Schnaubelt, 1998), often attributed to Afghan genetics.

5.6 Eudesmol Isomers

These isomers are bicyclic sesquiterpenoid alkene alcohols. Presence of both β- and γ-eudesmol isomers was judged to be characteristic of Afghani cannabis (Hillig & Mahlberg, 2004), or "indica" chemovars (Hazekamp et al., 2016).

Alpha-eudesmol inhibits calcium channels and was shown to attenuate neurogenic vasodilation, decrease dural extravasation, inhibit depolarization-evoked CGRP and substance P release from sensory nerve terminals without cardiovascular effects (Asakura et al., 2000), suggesting clinical application in migraine.

β-Eudesmol has been reported to be hepatoprotective against carbon-tetrachloride and galactosoamine-induced cytotoxicity in cultured rat hepatocytes (Kiso, Tohkin, & Hikino, 1983), and to inhibit electroshock-induced seizures in mice, additive to phenytoin (Chiou, Ling, & Chang, 1997). Other older reports (summarized in Li et al., 2013) note its ability to block nicotinic receptors at the neuromuscular junctions, display antiinflammatory effects, and antagonize toxicity related to organophosphate poisoning.

Recent investigation of β-eudesmol indicates its ability in mice to stimulate gastric emptying and intestinal motility via inhibition of dopamine D_2 and serotonin 5-HT_2 receptors in a dose-dependent fashion (25–100 mg/kg) (Kimura & Sumiyoshi, 2012).

Several reports document efficacy in cancer: β-eudesmol produced apoptosis in human leukemia HL60 cell culture, producing apoptosis via effects on JNK signaling in mitochondria (Li et al., 2013); both α- and β-eudesmol produced cytotoxic effects in low μg/mL concentrations in human hepatocellular carcinoma HepG2 cells with increase in caspase-3 activation, loss of mitochondrial membrane potential and apoptosis (D. S. Bomfim et al., 2013); β-eudesmol reduced human cholangiocarcinoma xenograft tumors in nude mice 91.6% at a dose of 100 mg/kg with prolongation of survival by 64.4% (Plengsuriyakarn, Karbwang, & Na-Bangchang, 2015); and it also inhibited proliferation of human lung A549 and colon HT29 and Caco-2

cells, superoxide synthesis in A549, and cell adhesion and migration in A549 and HT29 lines at high concentrations (100 μM) (Ben Sghaier et al., 2016). While it is unlikely that such concentrations would be attainable in herbal cannabis or concentrates, these results suggest possibilities for synergy with other cannabis components.

β-Eudesmol demonstrated BDI against *A. aegypti* of 0.81, and *A. quadrimaculatus* mosquitoes with BDI of 0.82, comparable to DEET at a concentration of 25 nM/cm^3, but was ineffective against larvae (Ali et al., 2015).

Additionally, β-eudesmol in low micromolar concentrations inhibited activity of histidine decarboxylase and mast cell degranulation in a human cell line, HMC-1 (Han et al., 2017), suggesting its possible application in treatment of allergies.

5.7 Nerolidol

Nerolidol, previously reviewed (Russo, 2011), is a noncyclic sesquiterpene alkene alcohol with sedative properties (Binet, Binet, Miocque, Roux, & Bernier, 1972; Lapczynski, Bhatia, Letizia, & Api, 2008), common to citrus peels. It reduced colon adenoma formation in rats (Wattenberg, 1991). It enhanced skin penetration of 5-fluorouracil (Cornwell & Barry, 1994), and it produced growth inhibition of dermophytes (Langenheim, 1994). Unlike some conventional cutaneous preparations, nerolidol is nontoxic and non-sensitizing (Lapczynski, Letizia, & Api, 2008). Potent antimalarial (Lopes et al., 1999; Rodrigues Goulart et al., 2004) and antileishmanial effects (Arruda, D'Alexandri, Katzin, & Uliana, 2005) have been noted, including an IC_{50} of 7.0 μM in a recent experiment (Camargos et al., 2014). Although present in Sativex®, it seems to exist at only minimal concentration in Californian chemovars (Giese et al., 2015).

5.8 Gurjunene

Gurjunene, a tricyclic sesquiterpene alkene, has also been reported in cannabis, but it is difficult to distinguish it analytically from nerolidol (Hazekamp et al., 2016). Gurjunene is common to EO of agarwood (*Aquilaria agallocha*) (Takemoto, Ito, Shiraki, Yagura, & Honda, 2008), and when administered as a vapor to mice it produced a biphasic dose-response, effectively reducing locomotor activity at 1.5%, but stimulating activity at 15% concentration.

5.9 γ-Cadinene

A bicyclic sesquiterpene, while more common in other EOs, cadinene is found in low concentration in current cannabis chemovars tested (Hazekamp et al., 2016). Cadinene demonstrated larvicidal activity against the *Anopholes stephensi*, vector of malaria (LC_{50} [lethal concentration] 8.23 μg/mL), *A. aegypti*, vector of dengue (LC_{50} 9.03 μg/mL), and *C. quinquefaciatus*, vector of filariasis (LC_{50} 9.86 μg/mL) (Govindarajan, Rajeswary, Hoti, et al., 2016; Govindarajan, Rajeswary, et al., 2016). Little pharmacology of the isolated compound is available, otherwise.

5.10 β-Farnesene

Trans-β-farnesene, an acyclic sesquiterpenes alkene, common to green apple and its scent, and some higher animals, is present in trace amounts in some cannabis chemovars, and was considered characteristic of "sativa" types (Hazekamp et al., 2016). Said to possess DPPH free radical scavenging, anticarcinogenic, antibacterial, and antifungal activity (Turkez et al., 2014), β-farnesene also demonstrated dose-related neuroprotective effects on cultured rat primary cortical neurons, blocking H_2O_2-induced intracellular LDH release and reduced DNA damage 47.8%, suggesting application in neurodegenerative diseases.

6. CANNABIS ODDS AND ENDS: ROOT TRITERPENOIDS AND ALKALOIDS, LEAF FLAVONOIDS, SEED COATS, AND SPROUTS (FIG. 5)

While it is clear that the unfertilized female flowering tops with their capitate glandular trichomes are the preeminent phytotherapeutic factory in cannabis, other parts of the plant produce distinctive chemistries of their own, and offer synergistic possibilities in cannabis combinations from this "pharmacological treasure trove" (Mechoulam, 2005). Considering that many parts of the plant are commonly discarded, these "extraneous" materials deserve much closer scrutiny and consideration.

6.1 Friedelin

While cannabis roots contain no phytocannabinoids (Potter, 2009), mono- or sesquiterpenoids, they do produce triterpenoids, the 30-carbon molecules that are the most diverse phytochemicals in nature, derived by cyclization of squalene. They display a wide spectrum of antiinflammatory, antipyretic,

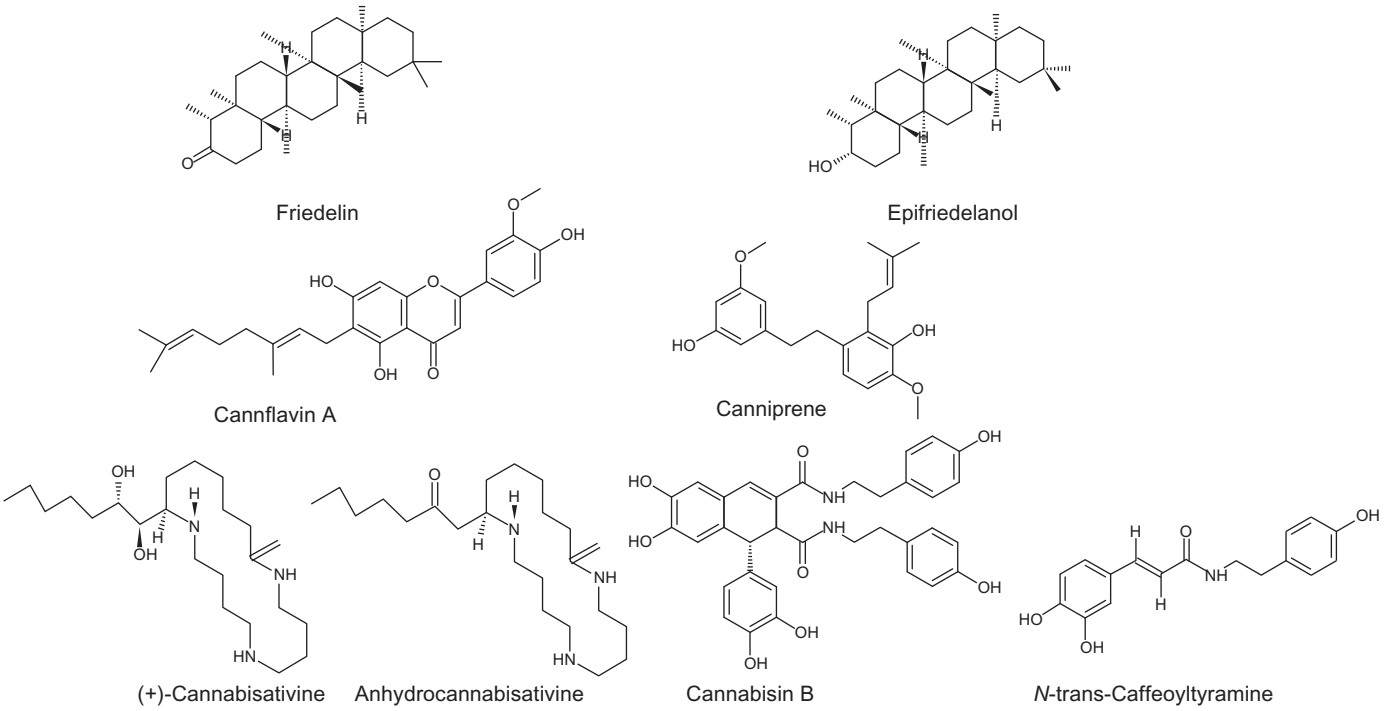


Fig. 5 Cannabis odds and ends: triterpenoids, alkaloids, flavonoids, bibenzyls, etc. (all structures drawn by EBR using ChemSketch 2015.2.5).

and anticarcinogenic effects with low toxicity (Bishayee, Ahmed, Brankov, & Perloff, 2011). Friedelin is the most prominent triterpenoid in cannabis. It was isolated in 1892 by Friedel, or as early as 1805, as "cerine" and found in many plants (*Aesculus, Cannabis*, *Citrus*, *Diospyros*, *Quercus*, *Rhododendron*, *Vaccinium*), algae, lichen, mosses, peat, coal, mineral wax, and swine (Chandler & Hooper, 1979). Its concentration in cannabis root was calculated as 12.8 mg/kg (Slatkin et al., 1971). Friedelin was weakly active (35 μM or above) against four cancer cell lines (Ee, Lim, Rahmat, & Lee, 2005). More promising were its antiinflammatory and antipyretic effects. In adult Wistar albino rats, friedelin markedly reduced carrageenan-induced hind paw edema, the effect persisting for 6 h (Antonisamy, Duraipandiyan, & Ignacimuthu, 2011). Results of friedelin at 40 mg/kg dose were comparable to those of indomethacin 10 mg/kg. In the same study, friedelin at doses of 2 or 4 mg markedly reduced rat ear edema after croton oil administration, inhibited peritoneal capillary permeability after acetic acid administration in a dose-related manner. Friedelin inhibited granuloma formation after placement of cotton pellets subcutaneously in the axillae, significantly ($P<0.05$) inhibited paw swelling after Freund's adjuvant injection, and significantly ($P<0.05$) reduced abdominal constrictions and stretching after acetic acid injection. The effect was less on first phase (0–5 min) neurogenic pain than on second phase (20–30 min) inflammatory pain. Friedelin showed no significant effect vs control on pain threshold in the hot-plate test. Friedelin administered orally showed significant reduction in rectal temperature ($P<0.05$) after yeast injection, results comparable to the antipyretic effect of paracetamol (acetaminophen).

Additionally, friedelin showed reducing power in vitro, comparable to BHT and ascorbate, which was dose-related (Sunil, Duraipandiyan, Ignacimuthu, & Al-Dhabi, 2013). In five in vitro antioxidant assays, the following results were noted at high concentrations: DPPH radical scavenging effect: IC_{50} at 21.1 mM, hydroxyl radical scavenging: 50% inhibition at 19.8 mM, nitric oxide radical inhibition: IC_{50} at 22.1 mM, superoxide radical scavenging: IC_{50} at 21.9 mM, inhibition of lipid peroxidation: IC_{50} at 18.1 mM. Friedelin 40 mg/kg pretreatment reduced CCl_4-induced LFT elevations due to hepatic damage ($P<0.005$), comparable to silymarin extract of *Silybum marianum* (milk thistle). Friedelin 40 mg/kg pretreatment before CCl_4 administration produced highly significant increases in superoxide dismutase, catalase, and glutathione peroxidase levels ($P<0.005$) to normal values, comparable to silymarin.

Friedelin demonstrated antimycobacterial activity against three nonpathogenic species at a MIC of 800 μg/mL and merited mention as a natural African antituberculosis agent (Chinsembu, 2016). Interestingly, this usage parallels that of cannabis leaf macerated in warm water and taken as a treatment for TB by the Bapedi healers of Limpopo Province, South Africa (Semenya, Potgieter, Tshisikhawe, Shava, & Maroyi, 2012), and certainly, friedelin may be contributing to any therapeutic benefit.

Friedelin was also effective in protecting against ethanol-induced gastric ulceration in rats (Antonisamy et al., 2015). Oral treatment at 35 mg/kg reduced gross and histological effects, increased mucosal PGE2 level 5.1-fold and NO 2.55-fold, as well as significantly reducing microvascular permeability. Friedelin increased gastric mucus content 3.12-fold and pH 4.03-fold vs control animals, also reducing DNA fragmentation and caspase-3 activity. Overall, the level of gastroprotection with friedelin scored 88.21% as compared to the standard drug, omeprazole, at 90.82%. Synergy of friedelin as a preventive of gastrointestinal ulcers would certainly be possible with reports of similar benefits attributed to THC (Douthwaite, 1947) and caryophyllene (Tambe, Tsujiuchi, Honda, Ikeshiro, & Tanaka, 1996).

6.2 Epifriedelanol

This closely related triterpenoid molecule had a measured concentration in cannabis root of 21.3 mg/kg (Slatkin et al., 1971). It was utilized to assess adriamycin-induced cell senescence in human fibroblasts (HDF) and HUVECs (Yang, Son, Jung, Zheng, & Kim, 2011), wherein epifriedelanol was especially active, and also decreased SA-β-gl activity, p53 protein, and ROS. The authors stated, "This compound [epifriedelanol] may be a promising candidate for developing dietary supplements or cosmetics to modulate tissue aging-associated diseases".

6.3 Cannabis Root Alkaloids: Cannabisativine and Anhydrocannabisativine

Cannabisativine was isolated from cannabis root (Lotter & Abraham, 1975; Slatkin, Knapp, Schiff, Turner, & Mole, 1975) with calculated concentrations of 2.5 mg/kg (Turner, Hsu, Knapp, Schiff, & Slatkin, 1976) or 0.0004% (Mechoulam et al., 1988). Anhydrocannabisativine was isolated from cannabis roots and leaves (Elsohly et al., 1978), at calculated concentrations of 0.3 mg/kg or 0.00046% (Mechoulam et al., 1988). No pharmacological information is available on either substance: "They are present in

miniscule amounts and are presumably not relevant to any cannabis biological activity" (Raphael, Personal comm. to EBR 2013).

6.4 Other Root Components

Slatkin (Slatkin et al., 1975) isolated additional compounds from cannabis root with methanol: sitosterol (calculated content 1.5%), campestrol (0.78%), stigmasterol (0.56%), choline, and neurine. The same author (Slatkin et al., 1971) isolated *N*(*p*-hydroxy-β-phenylethyl)-*p*-hydroxyl-*trans*-cinnamamide (1.6 mg/kg), with analgesic activity in the mouse tail flick test at 25, 50, and 100 mg/kg sc.

6.5 Cannabis Seeds

Cannabis or hemp seeds are possibly the single most nutritionally complete food on earth, and reportedly harbor powerful antiinflammatory effects. They contain 35% protein as the digestible edestin, and all essential amino acids. The seeds also contain 35% oil, rich in essential fatty acids in what is considered the ideal nutritional 3:1 ω6:ω3 ratio:75% linoleic acid (LA, ω-6), 25% linolenic acid (LNA, ω-3), and 9% gamma-linolenic acid (GLA, ω-6) (Callaway, 2004).

Hemp hulls, often discarded during manufacture of nutritional products, also contain interesting pharmacology. Two compounds were isolated from Chinese varieties (Chen et al., 2012). Antioxidant activity against DPPH radical revealed IC_{50} 9.42 μg/mL for *N*-*trans*-caffeoyltyramine and 11.17 μ/mL for cannabisin B, both higher than ariciresinol diglucoside (SDG) and soybean isoflones (ISO). Both compounds also showed prominent activity in inhibiting human LDL oxidation. In subsequent work (Chen et al., 2013), cannabisin B produced antiproliferative effects in HepG2 human hepatocarcinoma cells (dose dependently up to 500 μM) via arrest in the S phase, and induction of autophagic cell death via regulation of the AKT/mTOR pathway.

6.6 Cannabis Flavonoids

Cannflavin A (CFA) is a flavone unique to cannabis (aerial parts), but is very difficult to isolate and purify via crystallization from its isomer, cannflavin B. It inhibits PGE_2 30 times more powerfully than ASA and displays an antiinflammatory potency intermediate to that of aspirin and dexamethasone (Barrett, Scutt, & Evans, 1986). It remained little studied beyond this for many years, when it was noted to be produced in hemp seed sprouts of certain cultivars (Werz et al., 2014). CFA suppressed PGE_2, the primary

mediator of inflammation, and directly inhibited mPGES-1 (at 1.8 μM), a target in inflammation and cancer. Cannflavin A did not significantly inhibit COX-1 nor COX-2, thus potentially avoiding adverse events such as gastrointestinal bleeding, myocardial infarctions, and cerebrovascular accidents associated with the latter agents. The authors indicated that dual inhibition of mPGES-1 and 5-LO is considered the ideal profile to treat inflammatory conditions with fewest side effects.

Cannabis leaves contain about 1% total flavonoids, especially apigenin and quercetin (see McPartland & Russo, 2001 for additional review).

6.7 Cannabis Bibenzyl Compounds

Canniprene is an isoprenylated bibenzyl unique to cannabis (Allegrone et al., 2017), that can be vaporized and is potentially present in smoke. Potential antiinflammatory activity was demonstrated via inhibition of 5-LO (IC_{50} 0.4 μM) and COX/mPGES pathway (IC_{50} 10.1 μM). Related compounds, cannabispiranol and cannabispirenone, were seeming inactive. Canniprene concentration in 160 chemovars ranged trace amounts to more than 0.2% in cannabis leaves. While its concentration did not correlate with phytocannabinoid content or developmental stage of the cannabis plant, it did have a reciprocal relationship with cannflavin A. It will be fascinating to explore the ecological roles that these substances play, and the implications that they might harbor for therapeutic application.

7. CONCLUSION

This review has examined the complex and varied pharmacology of cannabis, a plant that should no longer be considered merely a vehicle for THC, but rather, a potential botanical drug mixture of great therapeutic value in consideration of its genetic plasticity and the promise of its many components. Clinical trials that examine synergistic effects of cannabis components are sorely needed, particularly in the area of phytocannabinoid–terpenoid interactions and to assess salient differences between cannabis chemovars attributable to their relative concentrations of entourage compounds.

CONFLICT OF INTEREST

Ethan Russo is Medical Director of PHYTECS, a biomedical research organization with an interest in therapeutic application of substances discussed in this publication.

Jahan Marcu is Chief Science Officer for Americans for Safe Access, a member-based organization working to ensure safe and legal access to cannabis therapeutic uses and research.

ACKNOWLEDGMENTS

The authors would like to thank John McPartland, whose guidance in planning, and selection of cannabis compounds was essential to this effort. Debbie Churgai, technical editor, Americans for Safe Access, kindly provided assistance in editing the manuscript.

REFERENCES

Ali, A., Tabanca, N., Demirci, B., Blythe, E. K., Ali, Z., Baser, K. H., et al. (2015). Chemical composition and biological activity of four salvia essential oils and individual compounds against two species of mosquitoes. *Journal of Agricultural and Food Chemistry*, *63*(2), 447–456. http://doi.org/10.1021/jf504976f.

Allegrone, G., Pollastro, F., Magagnini, G., Taglialatela-Scafati, O., Seegers, J., Koeberle, A., et al. (2017). The bibenzyl canniprene inhibit the production of pro-inflammatory eicosanoids and selectively accumulates in some cannabis strains. *Journal of Natural Products*, *80*(3), 731–734. http://dx.doi.org/10.1021/acs.jnatprod.6b01126.

Alozie, S. O., Martin, B. R., Harris, L. S., & Dewey, W. L. (1980). 3H-Δ9-tetrahydrocannabinol, 3H-cannabinol and 3H-cannabidiol: Penetration and regional distribution in rat brain. *Pharmacology, Biochemistry, and Behavior*, *12*(2), 217–221. http://doi.org/10.1016/0091-3057(80)90359-7.

Americans for Safe Access. (2016). *Medical access to cannabis for pain treatment*. Retrieved January 3, 2017, from http://www.safeaccessnow.org/medical_cannabis_access_for_pain_treatment.

Antonisamy, P., Duraipandiyan, V., Aravinthan, A., Al-Dhabi, N. A., Ignacimuthu, S., Choi, K. C., et al. (2015). Protective effects of friedelin isolated from Azima tetracantha Lam. against ethanol-induced gastric ulcer in rats and possible underlying mechanisms. *European Journal of Pharmacology*, *750*, 167–175. http://doi.org/10.1016/j.ejphar.2015.01.015.

Antonisamy, P., Duraipandiyan, V., & Ignacimuthu, S. (2011). Anti-inflammatory, analgesic and antipyretic effects of friedelin isolated from Azima tetracantha Lam. in mouse and rat models. *Journal of Pharmacy and Pharmacology*, *63*(8), 1070–1077. http://doi.org/10.1111/j.2042-7158.2011.01300.x.

Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., et al. (2008). Antibacterial cannabinoids from cannabis sativa: A structure–activity study. *Journal of Natural Products*, *71*(8), 1427–1430. http://doi.org/10.1021/np8002673.

Arruda, D. C., D'Alexandri, F. L., Katzin, A. M., & Uliana, S. R. (2005). Antileishmanial activity of the terpene nerolidol. *Antimicrobial Agents and Chemotherapy*, *49*(5), 1679–1687.

Asakura, K., Kanemasa, T., Minagawa, K., Kagawa, K., Yagami, T., Nakajima, M., et al. (2000). alpha-eudesmol, a P/Q-type Ca(2+) channel blocker, inhibits neurogenic vasodilation and extravasation following electrical stimulation of trigeminal ganglion. *Brain Research*, *873*(1), 94–101.

Aydin, E., Turkez, H., & Tasdemir, S. (2013). Anticancer and antioxidant properties of terpinolene in rat brain cells. *Arhiv za Higijenu Rada i Toksikologiju*, *64*(3), 415–424. http://doi.org/10.2478/10004-1254-64-2013-2365.

Backes, M. (2014). *Cannabis pharmacy: The practical guide to medical marijuana*. New York: Black Dog & Leventhal.

Baek, S., Kim, Y. O., Kwag, J. S., Choi, K. E., Jung, W. Y., & Han, D. S. (1998). Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Archives of Pharmacal Research*, *21*(3), 353–356.

Bahi, A., Al Mansouri, S., Al Memari, E., Al Ameri, M., Nurulain, S. M., & Ojha, S. (2014). β-Caryophyllene, a CB2 receptor agonist produces multiple behavioral changes relevant to anxiety and depression in mice. *Physiology & Behavior*, *135C*, 119–124. http://doi.org/10.1016/j.physbeh.2014.06.003.

Bai, J., Zheng, Y., Wang, G., & Liu, P. (2016). Protective effect of D-limonene against oxidative stress-induced cell damage in human lens epithelial cells via the p38 pathway. *Oxidative Medicine and Cellular Longevity*, *2016*, 5962832. http://doi.org/10.1155/2016/5962832.

Baldissera, M. D., Grando, T. H., Souza, C. F., Gressler, L. T., Stefani, L. M., da Silva, A. S., et al. (2016). In vitro and in vivo action of terpinen-4-ol, gamma-terpinene, and alpha-terpinene against Trypanosoma evansi. *Experimental Parasitology*, *162*, 43–48. http://doi.org/10.1016/j.exppara.2016.01.004.

Balvers, M. G. J., Verhoeckx, K. C. M., Bijlsma, S., Rubingh, C. M., Meijerink, J., Wortelboer, H. M., et al. (2012). Fish oil and inflammatory status alter the n-3 to n-6 balance of the endocannabinoid and oxylipin metabolomes in mouse plasma and tissues. *Metabolomics: Official Journal of the Metabolomic Society*, *8*(6), 1130–1147. http://doi.org/10.1007/s11306-012-0421-9.

Banerjee, S. P., Snyder, S. H., & Mechoulam, R. (1975). Cannabinoids: Influence on neurotransmitter uptake in rat brain synaptosomes. *Journal of Pharmacology and Experimental Therapeutics*, *194*(1), 74–81.

Barbosa, L. C., Filomeno, C. A., & Teixeira, R. R. (2016). Chemical variability and biological activities of Eucalyptus spp. essential oils. *Molecules (Basel, Switzerland)*, *21*(12), 33. http://doi.org/10.3390/molecules21121671.

Barrett, M. L., Scutt, A. M., & Evans, F. J. (1986). Cannflavin A and B, prenylated flavones from Cannabis sativa L. *Experientia*, *42*(4), 452–453.

Baser, K. H. C., & Buchbauer, G. (2016). *Handbook of essential oils: Science, technology, and applications* (2nd ed.). Boca Raton, FL: CRC Press.

Batista, P. A., de Paula Werner, M. F., Oliveira, E. C., Burgos, L., Pereira, P., da Silva Brum, L. F., et al. (2010). The antinociceptive effect of (-)-linalool in models of chronic inflammatory and neuropathic hypersensitivity in mice. *The Journal of Pain*, *11*(11), 1222–1229. http://doi.org/10.1016/j.jpain.2010.02.022.

Batista, P. A., Werner, M. F., Oliveira, E. C., Burgos, L., Pereira, P., Brum, L. F., et al. (2008). Evidence for the involvement of ionotropic glutamatergic receptors on the antinociceptive effect of (-)-linalool in mice. *Neuroscience Letters*, *440*(3), 299–303. http://doi.org/10.1016/j.neulet.2008.05.092.

Ben Amar, M. (2006). Cannabinoids in medicine: A review of their therapeutic potential. *Journal of Ethnopharmacology*, *105*(1–2), 1–25. http://doi.org/10.1016/j.jep.2006.02.001.

Ben Sghaier, M., Mousslim, M., Pagano, A., Ammari, Y., Luis, J., & Kovacic, H. (2016). beta-Eudesmol, a sesquiterpene from Teucrium ramosissimum, inhibits superoxide production, proliferation, adhesion and migration of human tumor cell. *Environmental Toxicology and Pharmacology*, *46*, 227–233. http://doi.org/10.1016/j.etap.2016.07.019.

Bento, A. F., Marcon, R., Dutra, R. C., Claudino, R. F., Cola, M., Leite, D. F. P., et al. (2011). β-Caryophyllene inhibits dextran sulfate sodium-induced colitis in mice through CB2 receptor activation and PPARγ pathway. *The American Journal of Pathology*, *178*(3), 1153–1166. http://doi.org/10.1016/j.ajpath.2010.11.052.

Bettarini, F., Borgonovi, G. E., Fiorani, T., Gagliardi, I., Caprioli, V., Massardo, P., et al. (1993). Antiparasitic compounds from East African plants: Isolation and biological activity of anonaine, matricarianol, canthin-6-one, and caryophyllene oxide. *Insect Science and Its Application*, *14*(1), 93–99.

Bhatia, S. P., Letizia, C. S., & Api, A. M. (2008). Fragrance material review on alpha-terpineol. *Food Chem Toxicol*, *46*(Suppl. 11), S280–S285. http://doi.org/10.1016/j.fct.2008.06.027.

Bhatia, S. P., McGinty, D., Letizia, C. S., & Api, A. M. (2008). Fragrance material review on fenchyl alcohol. *Food Chem Toxicol*, *46*(Suppl 11), S157–159. http://dx.doi.org/10.1016/j.fct.2008.06.047.

Binet, L., Binet, P., Miocque, M., Roux, M., & Bernier, A. (1972). Recherches sur les proprietes pharmcodynamiques (action sedative et action spasmolytique) de quelques alcools terpeniques aliphatiques. *Annales Pharmaceutiques Françaises*, *30*(9), 611–616.

Bishayee, A., Ahmed, S., Brankov, N., & Perloff, M. (2011). Triterpenoids as potential agents for the chemoprevention and therapy of breast cancer. *Frontiers in Bioscience (Landmark Edition)*, *16*, 980–996.

Bisogno, T., Hanus, L., De Petrocellis, L., Tchilibon, S., Ponde, D. E., Brandi, I., et al. (2001). Molecular targets for cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *The British Journal of Pharmacology*, *134*(4), 845–852.

Bisset, N. G., & Wichtl, M. (2004). *Herbal drugs and phytopharmaceuticals: A handbook for practice on a scientific basis* (3rd ed.). Stuttgart, Boca Raton: Medpharm Scientific Publishers; CRC Press.

Bolognini, D., Costa, B., Maione, S., Comelli, F., Marini, P., Di Marzo, V., et al. (2010). The plant cannabinoid Delta9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *British Journal of Pharmacology*, *160*(3), 677–687. http://doi.org/10.1111/j.1476-5381.2010.00756.x.

Bolognini, D., Rock, E. M., Cluny, N. L., Cascio, M. G., Limebeer, C. L., Duncan, M., et al. (2013). Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. *British Journal of Pharmacology*, *168*(6), 1456–1470. http://doi.org/10.1111/bph.12043.

Bomfim, D. S., Ferraz, R. P., Carvalho, N. C., Soares, M. B., Pinheiro, M. L., Costa, E. V., et al. (2013). Eudesmol isomers induce caspase-mediated apoptosis in human hepatocellular carcinoma HepG2 cells. *Basic & Clinical Pharmacology & Toxicology*, *113*(5), 300–306. http://doi.org/10.1111/bcpt.12097.

Bomfim, L. M., Menezes, L. R. A., Rodrigues, A. C. B. C., Dias, R. B., Rocha, C. A. G., Soares, M. B. P., et al. (2016). Antitumour activity of the microencapsulation of Annona vepretorum essential oil. *Basic & Clinical Pharmacology & Toxicology*, *118*(3), 208–213. http://doi.org/10.1111/bcpt.12488.

Bonamin, F., Moraes, T. M., Dos Santos, R. C., Kushima, H., Faria, F. M., Silva, M. A., et al. (2014). The effect of a minor constituent of essential oil from Citrus aurantium: The role of β-myrcene in preventing peptic ulcer disease. *Chemico-Biological Interactions*, *212*, 11–19. http://doi.org/10.1016/j.cbi.2014.01.009.

Bonesi, M., Menichini, F., Tundis, R., Loizzo, M. R., Conforti, F., Passalacqua, N. G., et al. (2010). Acetylcholinesterase and butyrylcholinesterase inhibitory activity of Pinus species essential oils and their constituents. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *25*(5), 622–628. http://doi.org/10.3109/14756360903389856.

Booth, J. K., Page, J. E., & Bohlmann, J. (2017). Terpene synthases from Cannabis sativa. *PLoS ONE*, *12*(3), e0173911. http://dx.doi.org/10.1371/journal.pone.0173911.

Buchbauer, G. (2010). Biological activities of essential oils. In K. H. C. Baser & G. Buchbauer (Eds.), *Handbook of essential oils: Science, technology, and applications* (pp. 235–280). Boca Raton, FL: CRC Press.

Buchbauer, G., Jirovetz, L., Jager, W., Plank, C., & Dietrich, H. (1993). Fragrance compounds and essential oils with sedative effects upon inhalation. *Journal of Pharmaceutical Sciences*, *82*(6), 660–664.

Brown, N. K., & Harvey, D. J. (1990). In vitro metabolism of cannabichromene in seven common laboratory animals. *Drug Metabolism and Disposition*, *18*(6), 1065–1070.

Calhoun, S. R., Galloway, G. P., & Smith, D. E. (1998). Abuse potential of dronabinol (Marinol). *Journal of Psychoactive Drugs*, *30*(2), 187–196. http://doi.org/10.1080/02791072.1998.10399689.

Callaway, J. C. (2004). Hempseed as a nutritional resource: An overview. *Euphytica*, *140*, 65–72.

Camargos, H. S., Moreira, R. A., Mendanha, S. A., Fernandes, K. S., Dorta, M. L., & Alonso, A. (2014). Terpenes increase the lipid dynamics in the Leishmania plasma membrane at concentrations similar to their IC50 values. *PloS One*, *9*(8). e104429. http://doi.org/10.1371/journal.pone.0104429.

Campbell, W. E., Gammon, D. W., Smith, P., Abrahams, M., & Purves, T. D. (1997). Composition and antimalarial activity in vitro of the essential oil of Tetradenia riparia. *Planta Medica*, *63*(3), 270–272.

Carrier, E. J., Auchampach, J. A., & Hillard, C. J. (2006). Inhibition of an equilibrative nucleoside transporter by cannabidiol: A mechanism of cannabinoid immunosuppression. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(20), 7895–7900.

Carson, C. F., & Riley, T. V. (1995). Antimicrobial activity of the major components of the essential oil of Melaleuca alternifolia. *The Journal of Applied Bacteriology*, *78*(3), 264–269.

Carvalho-Freitas, M. I., & Costa, M. (2002). Anxiolytic and sedative effects of extracts and essential oil from Citrus aurantium L. *Biological & Pharmaceutical Bulletin*, *25*(12), 1629–1633.

Cascio, M. G., Gauson, L. A., Stevenson, L. A., Ross, R. A., & Pertwee, R. G. (2010). Evidence that the plant cannabinoid cannabigerol is a highly potent α2-adrenoceptor agonist and moderately potent 5HT1A receptor antagonist. *British Journal of Pharmacology*, *159*(1), 129–141. http://doi.org/10.1111/j.1476-5381.2009.00515.x.

Cascio, M. G., & Pertwee, R. G. (2014). Known pharmacological actions of nine non-psychotropic phytocannabinoids. In R. G. Pertwee (Ed.), *Handbook of cannabis* (pp. 137–156). Oxford, UK: Oxford University Press. http://doi.org/10.1093/acprof:oso/9780199662685.003.0007.

Cascone, P., Iodice, L., Maffei, M. E., Bossi, S., Arimura, G.-I., & Guerrieri, E. (2015). Tobacco overexpressing β-ocimene induces direct and indirect responses against aphids in receiver tomato plants. *Journal of Plant Physiology*, *173*, 28–32. http://doi.org/10.1016/j.jplph.2014.08.011.

Cawthorne, M. A., Wargent, E., Zaibi, M., Stott, C., & Wright, S. (2007). The CB1 antagonist, delta-9-tetrahydrocannabivarin (THCV) has anti-obesity activity in dietary-induced obese (DIO) mice. In *Presented at the 17th annual symposium on the cannabinoids, Saint-Sauveur, Quebec* (p. 141). Canada: International Cannabinoid Research Society.

Chandler, R. F., & Hooper, S. N. (1979). Friedelin and associated triterpenoids. *Phytochemistry*, *18*, 711–724.

Chen, T., Hao, J., He, J., Zhang, J., Li, Y., Liu, R., et al. (2013). Cannabisin B induces autophagic cell death by inhibiting the AKT/mTOR pathway and S phase cell cycle arrest in HepG2 cells. *Food Chemistry*, *138*(2–3), 1034–1041. http://doi.org/10.1016/j.foodchem.2012.11.102.

Chen, W., Liu, Y., Li, M., Mao, J., Zhang, L., Huang, R., et al. (2015). Anti-tumor effect of alpha-pinene on human hepatoma cell lines through inducing G2/M cell cycle arrest. *Journal of Pharmacological Sciences*, *127*(3), 332–338. http://doi.org/10.1016/j.jphs.2015.01.008.

Chen, T., Wu, Y., Zhang, Y., Wang, B., Hu, Y., Wang, C., et al. (2012). Archaeobotanical study of ancient food and cereal remains at the Astana cemeteries, Xinxiang, China. *PloS One*, *7*(9), e45137. http://doi.org/10.1371/journal.pone.0045137.

Chidambara Murthy, K. N., Jayaprakasha, G. K., & Patil, B. S. (2012). D-limonene rich volatile oil from blood oranges inhibits angiogenesis, metastasis and cell death in human colon cancer cells. *Life Sciences*, *91*(11–12), 429–439. http://doi.org/10.1016/j.lfs.2012.08.016.

Chinsembu, K. C. (2016). Tuberculosis and nature's pharmacy of putative anti-tuberculosis agents. *Acta Tropica*, *153*, 46–56. http://doi.org/10.1016/j.actatropica.2015.10.004.

Chiou, L. C., Ling, J. Y., & Chang, C. C. (1997). Chinese herb constituent beta-eudesmol alleviated the electroshock seizures in mice and electrographic seizures in rat hippocampal slices. *Neuroscience Letters*, *231*(3), 171–174.

Choi, Y. J., Sim, W. C., Choi, H. K., Lee, S. H., & Lee, B. H. (2013). Alpha-Terpineol induces fatty liver in mice mediated by the AMP-activated kinase and sterol response element binding protein pathway. *Food and Chemical Toxicology*, *55*, 129–136. http://doi.org/10.1016/j.fct.2012.12.025.

Choi, H. S., Song, H. S., Ukeda, H., & Sawamura, M. (2000). Radical-scavenging activities of citrus essential oils and their components: Detection using 1,1-diphenyl-2-picrylhydrazyl. *Journal of Agricultural and Food Chemistry*, *48*(9), 4156–4161.

Ciftci, O., Oztanir, M. N., & Cetin, A. (2014). Neuroprotective effects of β-myrcene following global cerebral ischemia/reperfusion-mediated oxidative and neuronal damage in a C57BL/J6 mouse. *Neurochemical Research*, *39*(9), 1717–1723. http://doi.org/10.1007/s11064-014-1365-4.

Clarke, R. C., & Merlin, M. D. (2012). *Cannabis: Evolution and ethnobotany*. Berkeley: University of California Press.

Claussen, U., Von Spulak, F., & Korte, F. (1966). Zur chemischen klassifizierung von pflanzen—XXXI, haschisch—X: Cannabichromen, ein neuer haschisch-inhalts-stoff. *Tetrahedron*, *22*(4), 1477–1479. http://doi.org/10.1016/S0040-4020(01)99445-1.

Cluny, N. L., Keenan, C. M., Reimer, R. A., Le Foll, B., & Sharkey, K. A. (2015). Prevention of diet-induced obesity effects on body weight and gut microbiota in mice treated chronically with delta9-tetrahydrocannabinol. *PloS One*, *10*(12), e0144270. http://doi.org/10.1371/journal.pone.0144270.

Console-Bram, L., Marcu, J., & Abood, M. E. (2012). Cannabinoid receptors: Nomenclature and pharmacological principles. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *38*(1), 4–15. http://doi.org/10.1016/j.pnpbp.2012.02.009.

Cornwell, P. A., & Barry, B. W. (1994). Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. *The Journal of Pharmacy and Pharmacology*, *46*(4), 261–269.

d'Alessio, P. A., Ostan, R., Bisson, J. F., Schulzke, J. D., Ursini, M. V., & Bene, M. C. (2013). Oral administration of d-limonene controls inflammation in rat colitis and displays anti-inflammatory properties as diet supplementation in humans. *Life Sciences*, *92*(24–26), 1151–1156. http://doi.org/10.1016/j.lfs.2013.04.013.

Davis, W. M., & Hatoum, N. S. (1983). Neurobehavioral actions of cannabichromene and interactions with Δ9-tetrahydrocannabinol. *General Pharmacology: The Vascular System*, *14*(2), 247–252. http://doi.org/10.1016/0306-3623(83)90004-6.

DeLong, G. T., Wolf, C. E., Poklis, A., & Lichtman, A. H. (2010). Pharmacological evaluation of the natural constituent of Cannabis sativa, cannabichromene and its modulation by Δ(9)-tetrahydrocannabinol. *Drug and Alcohol Dependence*, *112*(1–2), 126–133. http://doi.org/10.1016/j.drugalcdep.2010.05.019.

de Meijer, E. P. M., Bagatta, M., Carboni, A., Crucitti, P., Moliterni, V. M. C., Ranalli, P., et al. (2003). The inheritance of chemical phenotype in Cannabis sativa L. *Genetics*, *163*(1), 335–346.

de Meijer, E. P. M., & Hammond, K. M. (2005). The inheritance of chemical phenotype in Cannabis sativa L. (II): Cannabigerol predominant plants. *Euphytica*, *145*, 189–198.

de Meijer, E. P. M., & Hammond, K. M. (2016). The inheritance of chemical phenotype in Cannabis sativa L. (V): Regulation of the propyl-/pentyl cannabinoid ratio, completion of a genetic model. *Euphytica*, *210*(2), 291–307. http://doi.org/10.1007/s10681-016-1721-3.

de Meijer, E. P. M., Hammond, K. M., & Micheler, M. (2009). The inheritance of chemical phenotype in Cannabis sativa L. (III): Variation in cannabichromene proportion. *Euphytica*, *165*, 293–311.

de Meijer, E., & Limited, G. P. (2011). Cannabis sativa plants rich in cannabichromene and its acid, extracts thereof and methods of obtaining extracts there from (12/936,947).

de Moura, N. F., Simionatto, E., Porto, C., Hoelzel, S. C., Dessoy, E. C., Zanatta, N., et al. (2002). Quinoline alkaloids, coumarins and volatile constituents of Helietta longifoliata. *Planta Medica*, *68*(7), 631–634.

de Oliveira, M. G., Marques, R. B., de Santana, M. F., Santos, A. B., Brito, F. A., Barreto, E. O., et al. (2012). Alpha-terpineol reduces mechanical hypernociception and inflammatory response. *Basic & Clinical Pharmacology & Toxicology*, *111*(2), 120–125. http://doi.org/10.1111/j.1742-7843.2012.00875.x.

De Petrocellis, L., & Di Marzo, V. (2010). Non-CB1, non-CB2 receptors for endocannabinoids, plant cannabinoids, and synthetic cannabimimetics: Focus on G-protein-coupled receptors and transient receptor potential channels. *Journal of Neuroimmune Pharmacology*, *5*(1), 103–121. http://doi.org/10.1007/s11481-009-9177-z.

De Petrocellis, L., Ligresti, A., Moriello, A. S., Allara, M., Bisogno, T., Petrosino, S., et al. (2011). Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology*, *163*(7), 1479–1494. http://dx.doi.org/10.1111/j.1476-5381.2010.01166.x.

De Petrocellis, L., Orlando, P., Moriello, A. S., Aviello, G., Stott, C., Izzo, A. A., et al. (2012). Cannabinoid actions at TRPV channels: Effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiologica*, *204*(2), 255–266. http://doi.org/10.1111/j.1748-1716.2011.02338.x.

De Petrocellis, L., Vellani, V., Schiano-Moriello, A., Marini, P., Magherini, P. C., Orlando, P., et al. (2008). Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. *The Journal of Pharmacology and Experimental Therapeutics*, *325*(3), 1007–1015. http://doi.org/10.1124/jpet.107.134809.

Deiana, S., Watanabe, A., Yamasaki, Y., Amada, N., Arthur, M., Fleming, S., et al. (2012). Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Delta(9)-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour. *Psychopharmacology (Berl)*, *219*(3), 859–873. http://dx.doi.org/10.1007/s00213-011-2415-0.

de Lago, E., & Fernández-Ruiz, J. (2007). Cannabinoids and neuroprotection in motor-related disorders. *CNS & Neurological Disorders Drug Targets*, *6*(6), 377–387. http://doi.org/10.2174/187152707783399210.

De-Oliveira, A. C., Ribeiro-Pinto, L. F., & Paumgartten, J. R. (1997). In vitro inhibition of CYP2B1 monooxygenase by beta-myrcene and other monoterpenoid compounds. *Toxicology Letters*, *92*(1), 39–46. http://doi.org/10.1016/S0378-4274(97)00034-9, S0378427497000349 [pii].

do Socorro, S. R. M. S., Mendonca-Filho, R. R., Bizzo, H. R., de Almeida Rodrigues, I., Soares, R. M., Souto-Padron, T., et al. (2003). Antileishmanial activity of a linalool-rich essential oil from Croton cajucara. *Antimicrobial Agents and Chemotherapy*, *47*(6), 1895–1901.

do Vale, T. G., Furtado, E. C., Santos, J. G., Jr., & Viana, G. S. (2002). Central effects of citral, myrcene and limonene, constituents of essential oil chemotypes from Lippia alba (Mill.) n.e. Brown. *Phytomedicine*, *9*(8), 709–714.

Dong, Y., Li, L., Wang, L., Zhou, T., Liu, J. W., & Gao, Y. J. (2015). Preliminary study of the effects of beta-elemene on MCF-7/ADM breast cancer stem cells. *Genetics and Molecular Research*, *14*(1), 2347–2355. http://doi.org/10.4238/2015.March.27.20.

Douthwaite, A. H. (1947). Choice of drugs in the treatment of duodenal ulcer. *British Medical Journal*, *2*(4514), 43–47.

Dussy, F. E., Hamberg, C., Luginbuhl, M., Schwerzmann, T., & Briellmann, T. A. (2005). Isolation of Delta9-THCA-A from hemp and analytical aspects concerning the determination of Delta9-THC in cannabis products. *Forensic Science International*, *149*(1), 3–10.

Edman, K., Lofstedt, H., Berg, P., Eriksson, K., Axelsson, S., Bryngelsson, I., et al. (2003). Exposure assessment to alpha- and beta-pinene, delta(3)-carene and wood dust in industrial production of wood pellets. *The Annals of Occupational Hygiene*, *47*(3), 219–226.

Ee, G. C., Lim, C. K., Rahmat, A., & Lee, H. L. (2005). Cytotoxic activities of chemical constituents from Mesua daphnifolia. *Tropical Biomedicine*, *22*(2), 99–102.

Elisabetsky, E., Marschner, J., & Souza, D. O. (1995). Effects of linalool on glutamatergic system in the rat cerebral cortex. *Neurochemical Research*, *20*(4), 461–465.

Elmann, A., Mordechay, S., Rindner, M., Larkov, O., Elkabetz, M., & Ravid, U. (2009). Protective effects of the essential oil of Salvia fruticosa and its constituents on astrocytic susceptibility to hydrogen peroxide-induced cell death. *Journal of Agricultural and Food Chemistry*, *57*(15), 6636–6641. http://doi.org/10.1021/jf901162f.

ElSohly, H. N., Turner, C. E., Clark, A. M., & Eisohly, M. A. (1982). Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. *Journal of Pharmaceutical Sciences*, *71*(12), 1319–1323.

Elsohly, M. A., Turner, C. E., Phoebe, C. H. J., Knapp, J. E., Schiff, P. L. J., & Slatkin, D. J. (1978). Anhydrocannabisativine, a new alkaloid from Cannabis sativa L. *Journal of Pharmaceutical Sciences*, *67*(1), 124.

Elzinga, S., Fischedick, J., Podkolinski, R., & Raber, J. C. (2015). Cannabinoid and terpenes as chemotaxonomic markers in cannabis. *Natural Products Chemistry & Research*, *3*(4), 1–9.

Evans, F. J. (1991). Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Medica*, *57*(7), S60–S67.

Evans, F. J. (2007). Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Medica*, *57*(S 1), S60–S67. http://doi.org/10.1055/s-2006-960231.

Falk, A. A., Hagberg, M. T., Lof, A. E., Wigaeus-Hjelm, E. M., & Wang, Z. P. (1990). Uptake, distribution and elimination of alpha-pinene in man after exposure by inhalation. *Scandinavian Journal of Work, Environment and Health*, *16*(5), 372–378.

Falk, A., Lof, A., Hagberg, M., Hjelm, E. W., & Wang, Z. (1991). Human exposure to 3-carene by inhalation: Toxicokinetics, effects on pulmonary function and occurrence of irritative and CNS symptoms. *Toxicology and Applied Pharmacology*, *110*(2), 198–205.

Falk-Filipsson, A., Lof, A., Hagberg, M., Hjelm, E. W., & Wang, Z. (1993). d-limonene exposure to humans by inhalation: Uptake, distribution, elimination, and effects on the pulmonary function. *Journal of Toxicology and Environmental Health*, *38*(1), 77–88.

Farag, R. S., Shalaby, A. S., El-Baroty, G. A., Ibrahim, N. A., Ali, M. A., & Hassan, E. M. (2004). Chemical and biological evaluation of the essential oils of different Melaleuca species. *Phytotherapy Research*, *18*(1), 30–35.

Fidyt, K., Fiedorowicz, A., & Strządała, L. (2016). β-caryophyllene and β-caryophyllene oxide—Natural compounds of anticancer and analgesic properties. *Cancer Medicine*, *5*(10), 3007–3017.

Fischedick, J. (2017). Indentification of terpenoid chemotypes among high (-)-*trans*-Δ^9-tetrahydrocannabinol-producing Cannabis sativa L. cultivars. *Cannabis and Cannabinoid Research*, *2.1*, 34–47. http://dx.doi.org/10.1089/can.2016.0040.

Fischedick, J. T., Hazekamp, A., Erkelens, T., Choi, Y. H., & Verpoorte, R. (2010). Metabolic fingerprinting of Cannabis sativa L., cannabinoids and terpenoids for chemotaxonomic and drug standardization purposes. *Phytochemistry*, *71*(17–18), 2058–2073. http://doi.org/10.1016/j.phytochem.2010.10.001.

Fischedick, J., Van Der Kooy, F., & Verpoorte, R. (2010). Cannabinoid receptor 1 binding activity and quantitative analysis of Cannabis sativa L. smoke and vapor. *Chemical & Pharmaceutical Bulletin*, *58*(2), 201–207.

Fitsiou, E., Anestopoulos, I., Chlichlia, K., Galanis, A., Kourkoutas, I., Panayiotidis, M. I., et al. (2016). Antioxidant and antiproliferative properties of the essential oils of Satureja thymbra and Satureja parnassica and their major constituents. *Anticancer Research*, *36*(11), 5757–5763. http://dx.doi.org/10.21873/anticanres.11159.

Flachenecker, P., Henze, T., & Zettl, U. K. (2014). Nabiximols (THC/CBD oromucosal spray, Sativex®) in clinical practice—Results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. *European Neurology*, *71*(5–6), 271–279. http://dx.doi.org/10.1159/000357427.

Formukong, E. A., Evans, A. T., & Evans, F. J. (1988). Analgesic and antiinflammatory activity of constituents of Cannabis sativa L. *Inflammation*, *12*(4), 361–371.

Franz, C., & Novak, J. (2010). Sources of essential oils. In K. H. C. Baser & G. Buchbauer (Eds.), *Handbook of essential oils: Science, technology, and applications* (pp. 39–82). Boca Raton, FL: CRC Press.

Fukumoto, S., Morishita, A., Furutachi, K., Terashima, T., Nakayama, T., & Yokogoshi, H. (2008). Effect of flavour components in lemon essential oil on physical or psychological stress. *Stress and Health*, *24*, 3–12.

Gaoni, Y., & Mechoulam, R. (1964). The structure and function of cannabigerol, a new hashish constituent. *Proceedings of the Chemical Society*, *1*, 82.

Gaoni, Y., & Mechoulam, R. (1966). Cannabichromene, a new active principle in hashish. *Chemical Communications (London)*, *1*, 20–21. http://doi.org/10.1039/C19660000020.

Gattefosse, R.-M. (1993). Gatefosse's aromatherapy (R. W. Tisserand, Trans.). Essex: C.W. Daniel.

Gauson, L. A., Stevenson, L. A., Thomas, A., Baillie, G. L., Ross, R. A., & Pertwee, R. G. (2007). Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors. In *Presented at the 17th annual symposium on the cannabinoids, Saint-Sauveur, Quebec* (p. 206). Canada: International Cannabinoid Research Society.

Gertsch, J. (2008). Anti-inflammatory cannabinoids in diet: Towards a better understanding of CB(2) receptor action? *Communicative & Integrative Biology*, *1*(1), 26–28.

Ghelardini, C., Galeotti, N., Salvatore, G., & Mazzanti, G. (1999). Local anaesthetic activity of the essential oil of Lavandula angustifolia. *Planta Medica*, *65*(8), 700–703. http://doi.org/10.1055/s-1999-14045.

Giese, M. W., Lewis, M. A., Giese, L., & Smith, K. M. (2015). Development and validation of a reliable and robust method for the analysis of cannabinoids and terpenes in cannabis. *Journal of AOAC International*, *98*(6), 1503–1522. http://doi.org/10.5740/jaoacint.15-116.

Gil, M. L., Jimenez, J., Ocete, M. A., Zarzuelo, A., & Cabo, M. M. (1989). Comparative study of different essential oils of Bupleurum gibraltaricum Lamarck. *Pharmazie*, *44*(4), 284–287.

Girola, N., Figueiredo, C. R., Farias, C. F., Azevedo, R. A., Ferreira, A. K., Teixeira, S. F., et al. (2015). Camphene isolated from essential oil of Piper cernuum (Piperaceae) induces intrinsic apoptosis in melanoma cells and displays antitumor activity in vivo. *Biochemical and Biophysical Research Communications*, *467*(4), 928–934. http://doi.org/10.1016/j.bbrc.2015.10.041.

Gong, M., Liu, Y., Zhang, J., Gao, Y. J., Zhai, P. P., Su, X., et al. (2015). beta-Elemene inhibits cell proliferation by regulating the expression and activity of topoisomerases I and IIalpha in human hepatocarcinoma HepG-2 cells. *BioMed Research International*, *2015*, 153987. http://doi.org/10.1155/2015/153987.

Govindarajan, M., Rajeswary, M., & Benelli, G. (2016). Delta-Cadinene, Calarene and delta-4-Carene from Kadsura heteroclita essential oil as novel larvicides against malaria, dengue and filariasis mosquitoes. *Combinatorial Chemistry & High Throughput Screening*, *19*(7), 565–571.

Govindarajan, M., Rajeswary, M., Hoti, S. L., Bhattacharyya, A., & Benelli, G. (2016). Eugenol, alpha-pinene and beta-caryophyllene from Plectranthus barbatus essential oil as eco-friendly larvicides against malaria, dengue and Japanese encephalitis mosquito vectors. *Parasitology Research*, *115*(2), 807–815. http://dx.doi.org/10.1007/s00436-015-4809-0.

Grassmann, J., Hippeli, S., Spitzenberger, R., & Elstner, E. F. (2005). The monoterpene terpinolene from the oil of Pinus mugo L. in concert with alpha-tocopherol and beta-carotene effectively prevents oxidation of LDL. *Phytomedicine*, *12*(6–7), 416–423.

Grotenhermen, F., Russo, E. B., & Zuardi, A. W. (2017). Even high doses of oral cannabidiol do not cause THC-like effects in humans. *Cannabis and Cannabinoid Research*, *2.1*, 1–4. http://dx.doi.org/10.1089/can.2016.0036.

Grunfeld, Y., & Edery, H. (1969). Psychopharmacological activity of the active constituents of hashish and some related cannabinoids. *Psychopharmacologia*, *14*(3), 200–210.

Grunfeld, E., & Gresty, M. A. (1998). Relationship between motion sickness, migraine and menstruation in crew members of a "round the world" yacht race. *Brain Research Bulletin*, *47*(5), 433–436.

Guy, G. W., & Stott, C. G. (2005). The development of Sativex- a natural cannabis-based medicine. In R. Mechoulam (Ed.), *Cannabinoids as therapeutics* (pp. 231–263). Basel, Switzerland: Birkhäuser Verlag.

Hampson, A. J., Grimaldi, M., Axelrod, J., & Wink, D. (1998). Cannabidiol and (-)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(14), 8268–8273.

Han, H. D., Cho, Y.-J., Cho, S. K., Byeon, Y., Jeon, H. N., Kim, H.-S., et al. (2016). Linalool-incorporated nanoparticles as a novel anticancer agent for epithelial ovarian carcinoma. *Molecular Cancer Therapeutics*, *15*(4), 618–627. http://doi.org/10.1158/1535-7163.MCT-15-0733-T.

Han, N. R., Moon, P. D., Ryu, K. J., Jang, J. B., Kim, H. M., & Jeong, H. J. (2017). Beta-eudesmol suppresses allergic reactions via inhibiting mast cell degranulation. *Clinical and Experimental Pharmacology and Physiology*, *44*(2), 257–265. http://dx.doi.org/10.1111/1440-1681.12698.

Hanus, L. O., Meyer, S. M., Munoz, E., Taglialatela-Scafati, O., & Appendino, G. (2016). Phytocannabinoids: A unified critical inventory. *Natural Product Reports*, *33*(12), 1357–1392. http://dx.doi.org/10.1039/c6np00074f.

Harris, B. (2010). Phytotherapeutic uses of essential oils. In K. H. C. Baser & G. Buchbauer (Eds.), *Handbook of essential oils: Science, technology, and applications* (pp. 315–352). Boca Raton: CRC Press.

Hassan, S. B., Gali-Muhtasib, H., Goransson, H., & Larsson, R. (2010). Alpha terpineol: A potential anticancer agent which acts through suppressing NF-kappaB signalling. *Anticancer Research*, *30*(6), 1911–1919.

Hazekamp, A., & Grotenhermen, F. (2010). Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids*, *5*(Special), 1–21.

Hazekamp, A., Tejkalová, K., & Papadimitriou, S. (2016). Cannabis: From cultivar to chemovar II—A metabolomics approach to cannabis classification. *Cannabis and Cannabinoid Research*, *1*(1), 202–215. http://doi.org/10.1089/can.2016.0017.

Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., et al. (1990). Cannabinoid receptor localization in brain. *Proceedings of the National Academy of Sciences of the United States of America*, *87*(5), 1932–1936.

Hill, A. J., Weston, S. E., Jones, N. A., Smith, I., Bevan, S. A., Williamson, E. M., et al. (2010). Delta-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia*, *51*(8), 1522–1532. http://doi.org/10.1111/j.1528-1167.2010.02523.x.

Hillig, K. W., & Mahlberg, P. G. (2004). A chemotaxonomic analysis of cannabinoid variation in Cannabis (Cannabaceae). *American Journal of Botany*, *91*(6), 966–975. http://doi.org/10.3732/ajb.91.6.966.

Hofmann, M. E., & Frazier, C. J. (2013). Marijuana, endocannabinoids, and epilepsy: Potential and challenges for improved therapeutic intervention. *Experimental Neurology*, *244*, 43–50. http://doi.org/10.1016/j.expneurol.2011.11.047.

Holley, J. H., Hadley, K. W., & Turner, C. E. (1975). Constituents of *Cannabis sativa* L. XI: Cannabidiol and cannabichromene in samples of known geographical origin. *Journal of Pharmaceutical Sciences*, *64*(5), 892–894.

Holland, M. L., Allen, J. D., & Arnold, J. C. (2008). Interaction of plant cannabinoids with the multidrug transporter ABCC1 (MRP1). *European Journal of Pharmacology*, *591*(1–3), 128–131. http://doi.org/10.1016/j.ejphar.2008.06.079.

Hong, P., & Liu, Y. (2017). Calcitonin gene-related peptide antagonism for acute treatment of migraine: A meta-analysis. *The International Journal of Neuroscience*, *127*(1), 20–27. http://doi.org/10.3109/00207454.2015.1137915.

Horváth, B., Mukhopadhyay, P., Haskó, G., & Pacher, P. (2012). The endocannabinoid system and plant-derived cannabinoids in diabetes and diabetic complications. *The American Journal of Pathology*, *180*(2), 432–442. http://doi.org/10.1016/j.ajpath.2011.11.003.

Hsieh, L. C., Hsieh, S. L., Chen, C. T., Chung, J. G., Wang, J. J., & Wu, C. C. (2015). Induction of alpha-phellandrene on autophagy in human liver tumor cells. *The American Journal of Chinese Medicine*, *43*(1), 121–136. http://doi.org/10.1142/S0192415X15500081.

Hsieh, S. L., Li, Y. C., Chang, W. C., Chung, J. G., Hsieh, L. C., & Wu, C. C. (2014). Induction of necrosis in human liver tumor cells by alpha-phellandrene. *Nutrition and Cancer*, *66*(6), 970–979. http://doi.org/10.1080/01635581.2014.936946.

Hu, Z., Wu, H., Li, Y., Hou, Q., Wang, Y., Li, S., et al. (2015). Beta-elemene inhibits the proliferation of esophageal squamous cell carcinoma by regulating long noncoding RNA-mediated inhibition of hTERT expression. *Anti-Cancer Drugs*, *26*(5), 531–539. http://doi.org/10.1097/CAD.0000000000000216.

Ismail, M. (2006). Central properties and chemical composition of Ocimum basilicum essential oil. *Pharmaceutical Biology*, *44*(8), 619–626.

Ito, K., & Ito, M. (2013). The sedative effect of inhaled terpinolene in mice and its structure-activity relationships. *Journal of Natural Medicines*, *67*(4), 833–837. http://doi.org/10.1007/s11418-012-0732-1.

Iwata, N., & Kitanaka, S. (2011). New cannabinoid-like chromane and chromene derivatives from Rhododendron anthopogonoides. *Chemical & Pharmaceutical Bulletin*, *59*(11), 1409–1412.

Jeong, J. G., Kim, Y. S., Min, Y. K., & Kim, S. H. (2008). Low concentration of 3-carene stimulates the differentiation of mouse osteoblastic MC3T3-E1 subclone 4 cells. *Phytotherapy Research*, *22*(1), 18–22. http://doi.org/10.1002/ptr.2247.

Jiang, S., Ling, C., Li, W., Jiang, H., Zhi, Q., & Jiang, M. (2016). Molecular mechanisms of anti-cancer activities of β-elemene: Targeting hallmarks of cancer. *Anti-Cancer Agents in Medicinal Chemistry*, *16*(11), 1426–1434.

Jianjun, Q., Song, Z., Yin, L., Jia, Z., & Donglei, L. (2008). Treatment of chylothorax with elemene. *The Thoracic and Cardiovascular Surgeon*, *56*(2), 103–105. http://doi.org/10.1055/s-2007-965708.

Jung, J., Kempf, J., Mahler, H., & Weinmann, W. (2007). Detection of Delta9-tetrahydrocannabinolic acid A in human urine and blood serum by LC-MS/MS. *Journal of Mass Spectrometry*, *42*(3), 354–360. http://doi.org/10.1002/jms.1167.

Kasanen, J. P., Pasanen, A. L., Pasanen, P., Liesivuori, J., Kosma, V. M., & Alarie, Y. (1999). Evaluation of sensory irritation of delta3-carene and turpentine, and acceptable levels of monoterpenes in occupational and indoor environment. *Journal of Toxicology and Environmental Health. Part A*, *57*(2), 89–114.

Kasuya, H., Okada, N., Kubohara, M., Satou, T., Masuo, Y., & Koike, K. (2015). Expression of BDNF and TH mRNA in the brain following inhaled administration of alpha-pinene. *Phytotherapy Research*, *29*(1), 43–47. http://doi.org/10.1002/ptr.5224.

Katsuyama, S., Mizoguchi, H., Kuwahata, H., Komatsu, T., Nagaoka, K., Nakamura, H., et al. (2013). Involvement of peripheral cannabinoid and opioid receptors in beta-caryophyllene-induced antinociception. *European Journal of Pain (London, England)*, *17*(5), 664–675. http://doi.org/10.1002/j.1532-2149.2012.00242.x.

Kennell, J. (2016). *A beekeeper has trained bees to make honey from cannabis resin*. Retrieved January 22, 2017, from http://thescienceexplorer.com/nature/beekeeper-has-trained-bees-make-honey-cannabis-resin.

Kim, S. S., Baik, J. S., Oh, T. H., Yoon, W. J., Lee, N. H., & Hyun, C. G. (2008). Biological activities of Korean Citrus obovoides and Citrus natsudaidai essential oils against acne-inducing bacteria. *Bioscience, Biotechnology, and Biochemistry*, *72*(10), 2507–2513.

Kim, S., Choi, Y., Choi, S., Choi, Y., & Park, T. (2014). Dietary camphene attenuates hepatic steatosis and insulin resistance in mice. *Obesity (Silver Spring)*, *22*(2), 408–417. http://doi.org/10.1002/oby.20554.

Kim, S. Y., Hwang, J. Y., & Shin, U. S. (2016). Preparation of nano/macroporous polycaprolactone microspheres for an injectable cell delivery system using room temperature ionic liquid and camphene. *Journal of Colloid and Interface Science*, *465*, 18–25. http://doi.org/10.1016/j.jcis.2015.11.055.

Kim, J. T., Ren, C. J., Fielding, G. A., Pitti, A., Kasumi, T., Wajda, M., et al. (2007). Treatment with lavender aromatherapy in the post-anesthesia care unit reduces opioid requirements of morbidly obese patients undergoing laparoscopic adjustable gastric banding. *Obesity Surgery*, *17*(7), 920–925.

Kimura, Y., & Sumiyoshi, M. (2012). Effects of an Atractylodes lancea rhizome extract and a volatile component beta-eudesmol on gastrointestinal motility in mice. *Journal of Ethnopharmacology*, *141*(1), 530–536. http://doi.org/10.1016/j.jep.2012.02.031.

Kiso, Y., Tohkin, M., & Hikino, H. (1983). Antihepatotoxic principles of Atractylodes rhizomes. *Journal of Natural Products*, *46*(5), 651–654.

Komiya, M., Takeuchi, T., & Harada, E. (2006). Lemon oil vapor causes an anti-stress effect via modulating the 5-HT and DA activities in mice. *Behavioural Brain Research*, *172*(2), 240–249. http://doi.org/10.1016/j.bbr.2006.05.006.

Komori, T., Fujiwara, R., Tanida, M., Nomura, J., & Yokoyama, M. M. (1995). Effects of citrus fragrance on immune function and depressive states. *Neuroimmunomodulation*, *2*(3), 174–180.

Kose, E. O., Deniz, I. G., Sarikurkcu, C., Aktas, O., & Yavuz, M. (2010). Chemical composition, antimicrobial and antioxidant activities of the essential oils of Sideritis erythrantha Boiss. and Heldr. (var. erythrantha and var. cedretorum P.H. Davis) endemic in Turkey. *Food and Chemical Toxicology*, *48*(10), 2960–2965. http://dx.doi.org/10.1016/j.fct.2010.07.033.

Kovac, J., Simunovic, K., Wu, Z., Klancnik, A., Bucar, F., Zhang, Q., et al. (2015). Antibiotic resistance modulation and modes of action of (-)-alpha-pinene in Campylobacter jejuni. *PloS One*, *10*(4), e0122871. http://doi.org/10.1371/journal.pone.0122871.

Kowal, M. A., Hazekamp, A., & Grotenhermen, F. (2016). Review on clinical studies with cannabis and cannabinoids 2010-2014. *Cannabinoids*, *11*(Special), 1–18.

Krol, S., Namiesnik, J., & Zabiegala, B. (2014). alpha-Pinene, 3-carene and d-limonene in indoor air of Polish apartments: The impact on air quality and human exposure. *The Science of the Total Environment*, *468–469*, 985–995. http://doi.org/10.1016/j.scitotenv.2013.08.099.

Kusuhara, M., Urakami, K., Masuda, Y., Zangiacomi, V., Ishii, H., Tai, S., et al. (2012). Fragrant environment with alpha-pinene decreases tumor growth in mice. *Biomedical Research*, *33*(1), 57–61.

Lafourcade, M., Larrieu, T., Mato, S., Duffaud, A., Sepers, M., Matias, I., et al. (2011). Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. *Nature Neuroscience*, *14*(3), 345–350. http://doi.org/10.1038/nn.2736.

Lafuente, H., Alvarez, F. J., Pazos, M. R., Alvarez, A., Rey-Santano, M. C., Mielgo, V., et al. (2011). Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs. *Pediatric Research*, *70*(3), 272–277. http://doi.org/10.1203/PDR.0b013e3182276b11.

Langenheim, J. H. (1994). Higher plant terpenoids: A phytocentric overview of their ecological roles. *Journal of Chemical Ecology*, *20*(6), 1223–1279.

Lapczynski, A., Bhatia, S. P., Letizia, C. S., & Api, A. M. (2008). Fragrance material review on nerolidol (isomer unspecified). *Food Chem Toxicol*, *46*(Suppl. 11), S247–S250. http://dx.doi.org/10.1016/j.fct.2008.06.063. S0278-6915(08)00355-4 [pii].

Lapczynski, A., Letizia, C. S., & Api, A. M. (2008). Addendum to Fragrance material review on linalool. *Food and Chemical Toxicology*, *46*(Suppl. 11), S190–S192.

Laprairie, R. B., Bagher, A. M., Kelly, M. E. M., & Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the type 1 cannabinoid receptor. *British Journal of Pharmacology*, *172*(20), 4790–4805. http://doi.org/10.1111/bph.13250.

Lastbom, L., Boman, A., Johnsson, S., Camner, P., & Ryrfeldt, A. (2003). Increased airway responsiveness of a common fragrance component, 3-carene, after skin sensitisation—A study in isolated guinea pig lungs. *Toxicology Letters*, *145*(2), 189–196.

Lawless, J. (1995). *The illustrated encyclopedia of essential oils: The complete guide to the use of oils in aromatherapy and herbalism*. Shaftesbury, Dorset, [England]; Rockport, Mass: Element.

Leal-Cardoso, J. H., da Silva-Alves, K. S., Ferreira-da-Silva, F. W., dos Santos-Nascimento, T., Joca, H. C., de Macedo, F. H. P., et al. (2010). Linalool blocks excitability in peripheral nerves and voltage-dependent Na+ current in dissociated dorsal root ganglia neurons. *European Journal of Pharmacology*, *645*(1–3), 86–93.

Legault, J., & Pichette, A. (2007). Potentiating effect of β-caryophyllene on anticancer activity of α-humulene, isocaryophyllene and paclitaxel. *Journal of Pharmacy and Pharmacology*, *59*(12), 1643–1647. http://doi.org/10.1211/jpp.59.12.0005.

Li, Q., Li, L., Wang, F., CHEN, J., Zhao, Y., Wang, P., et al. (2013). Dietary capsaicin prevents nonalcoholic fatty liver disease through transient receptor potential vanilloid 1-mediated peroxisome proliferator-activated receptor delta activation. *Pflügers Archiv: European Journal of Physiology*, *465*(9), 1303–1316. http://doi.org/10.1007/s00424-013-1274-4.

Li, L., Shi, C., Yin, Z., Jia, R., Peng, L., Kang, S., et al. (2014). Antibacterial activity of alpha-terpineol may induce morphostructural alterations in Escherichia coli. *Brazilian Journal of Microbiology*, *45*(4), 1409–1413.

Lichtman, A. H., Sheikh, S. M., Loh, H. H., & Martin, B. R. (2001). Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice. *Journal of Pharmacology and Experimental Therapeutics*, *298*(3), 1007–1014.

Ligresti, A., Moriello, A. S., Starowicz, K., Matias, I., Pisanti, S., De Petrocellis, L., et al. (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *Journal of Pharmacology and Experimental Therapeutics*, *318*(3), 1375–1387. http://doi.org/10.1124/jpet.106.105247.

Lima, D. F., Brandao, M. S., Moura, J. B., Leitao, J. M., Carvalho, F. A., Miura, L. M., et al. (2012). Antinociceptive activity of the monoterpene alpha-phellandrene in rodents: Possible mechanisms of action. *Journal of Pharmacy and Pharmacology*, *64*(2), 283–292. http://doi.org/10.1111/j.2042-7158.2011.01401.x.

Lin, W. Y., Kuo, Y. H., Chang, Y. L., Teng, C. M., Wang, E. C., Ishikawa, T., et al. (2003). Anti-platelet aggregation and chemical constituents from the rhizome of Gynura japonica. *Planta Medica*, *69*(8), 757–764.

Lin, J. J., Lin, J. H., Hsu, S. C., Weng, S. W., Huang, Y. P., Tang, N. Y., et al. (2013). Alpha-phellandrene promotes immune responses in normal mice through enhancing macrophage phagocytosis and natural killer cell activities. *In Vivo*, *27*(6), 809–814.

Lin, J. J., Wu, C. C., Hsu, S. C., Weng, S. W., Ma, Y. S., Huang, Y. P., et al. (2015). Alpha-phellandrene-induced DNA damage and affect DNA repair protein expression in WEHI-3 murine leukemia cells in vitro. *Environmental Toxicology*, *30*(11), 1322–1330. http://doi.org/10.1002/tox.22003.

Lin, J. J., Yu, C. C., Lu, K. W., Chang, S. J., Yu, F. S., Liao, C. L., et al. (2014). alpha-Phellandrene alters expression of genes associated with DNA damage, cell cycle, and apoptosis in murine leukemia WEHI-3 cells. *Anticancer Research*, *34*(8), 4161–4180.

Liu, J. S., Che, X. M., Chang, S., Qiu, G. L., He, S. C., Fan, L., et al. (2015). beta-elemene enhances the radiosensitivity of gastric cancer cells by inhibiting Pak1 activation. *World Journal of Gastroenterology*, *21*(34), 9945–9956. http://doi.org/10.3748/wjg.v21.i34.9945.

Liu, T., Wang, C. J., Xie, H. Q., & Mu, Q. (2013). Guaiol–a naturally occurring insecticidal sesquiterpene. *Natural Product Communications*, *8*(10), 1353–1354.

Liu, J., Zhang, Z., Gao, J., Xie, J., Yang, L., & Hu, S. (2011). Downregulation effects of beta-elemene on the levels of plasma endotoxin, serum TNF-alpha, and hepatic CD14 expression in rats with liver fibrosis. *Frontiers in Medicine*, *5*(1), 101–105. http://doi.org/10.1007/s11684-011-0111-4.

Lone, J., & Yun, J. W. (2016). Monoterpene limonene induces brown fat-like phenotype in 3T3-L1 white adipocytes. *Life Sciences*, *153*, 198–206. http://doi.org/10.1016/j.lfs.2016.04.010.

Lopes, N. P., Kato, M. J., Andrade, E. H., Maia, J. G., Yoshida, M., Planchart, A. R., et al. (1999). Antimalarial use of volatile oil from leaves of Virola surinamensis (Rol.) Warb. by Waiapi Amazon Indians. *Journal of Ethnopharmacology*, *67*(3), 313–319.

Lorenzetti, B. B., Souza, G. E., Sarti, S. J., Santos Filho, D., & Ferreira, S. H. (1991). Myrcene mimics the peripheral analgesic activity of lemongrass tea. *Journal of Ethnopharmacology*, *34*(1), 43–48.

Lotter, H. L., & Abraham, D. J. (1975). Cannabisativine, a new alkaloid from Cannabis sativa L. root. *Tetrahedron Letters*, *16*(33), 2815–2818.

Lowette, K., Roosen, L., Tack, J., & Berghe, P. V. (2015). Effects of high-fructose diets on central appetite signaling and cognitive function. *Frontiers in Nutrition*, *2*, 1–5. http://doi.org/10.3389/fnut.2015.00005/abstract.

Macedo, E. M., Santos, W. C., Sousa, B. P. N., Lopes, E. M., Piauilino, C. A., Cunha, F. V., et al. (2016). Association of terpinolene and diclofenac presents antinociceptive and anti-inflammatory synergistic effects in a model of chronic inflammation. *Brazilian Journal of Medical and Biological Research = Revista Brasileira De Pesquisas Médicas E Biológicas/ Sociedade Brasileira De Biofísica … [Et Al.]*, *49*(7), 10. http://doi.org/10.1590/1414-431X20165103.

Maione, S., Piscitelli, F., Gatta, L., Vita, D., De Petrocellis, L., Palazzo, E., et al. (2011). Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action. *British Journal of Pharmacology*, *162*(3), 584–596. http://doi.org/10.1111/j.1476-5381.2010.01063.x.

Maisonnasse, A., Lenoir, J.-C., Beslay, D., Crauser, D., & Le Conte, Y. (2010). E-β-ocimene, a volatile brood pheromone involved in social regulation in the honey bee colony (Apis mellifera). *PloS One*, *5*(10), e13531. http://doi.org/10.1371/journal.pone.0013531.

Maor, Y., Gallily, R., & Mechoulam, R. (2006). The relevance of the steric factor in the biological activity of CBD derivatives-a tool in identifying novel molecular target for cannabinoids. In *Presented at the symposium on the cannabinoids, Tihany* (p. 1). Hungary: International Cannabinoid Research Society.

Marcu, J. P. (2016). An overview of major and minor phytocannabinoids. In V. R. Preedy (Ed.), Neuropathology of drug addictions and substance misuse (pp. 672–678). Elsevier Academic Press: Amsterdam; Boston, MA. http://doi.org/10.1016/B978-0-12-800213-1.00062-6.

Marcu, J. P., Christian, R. T., Lau, D., Zielinski, A. J., Horowitz, M. P., Lee, J., et al. (2010). Cannabidiol enhances the inhibitory effects of 9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Molecular Cancer Therapeutics*, *9*(1), 180–189. http://doi.org/10.1158/1535-7163.MCT-09-0407.

Martin, B. R., Compton, D. R., Thomas, B. F., Prescott, W. R., Little, P. J., Razdan, R. K., et al. (1991). Behavioral, biochemical, and molecular modeling evaluations of

cannabinoid analogs. *Pharmacology, Biochemistry, and Behavior*, *40*(3), 471–478. http://doi.org/10.1016/0091-3057(91)90349-7.

Martin-Moreno, A. M., Reigada, D., Ramirez, B. G., Mechoulam, R., Innamorato, N., Cuadrado, A., et al. (2011). Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: Relevance to Alzheimer's disease. *Molecular Pharmacology*, *79*(6), 964–973. http://doi.org/10.1124/mol.111.071290.

Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C., & Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature*, *346*(6284), 561–564. http://doi.org/10.1038/346561a0.

McLaughlin, P. J. (2012). Reports of the death of CB1 antagonists have been greatly exaggerated. *Behavioural Pharmacology*, *23*(5–6), 537–550. http://doi.org/10.1097/FBP.0b013e3283566a8c.

McPartland, J. M., Duncan, M., Di Marzo, V., & Pertwee, R. G. (2015). Are cannabidiol and Delta(9)-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. *British Journal of Pharmacology*, *172*(3), 737–753. http://doi.org/10.1111/bph.12944.

McPartland, J. M., Guy, G. W., & Di Marzo, V. (2014). Care and feeding of the endocannabinoid system: A systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PloS One*, *9*(3), e89566. http://doi.org/10.1371/journal.pone.0089566.

McPartland, J. M., & Russo, E. B. (2001). Cannabis and cannabis extracts: Greater than the sum of their parts? *Journal of Cannabis Therapeutics*, *1*(3–4), 103–132. http://doi.org/10.1300/J175v01n03_08.

McPartland, J. M., & Russo, E. B. (2014). Non-phytocannabinoid constituents of cannabis and herbal synergy. *Handbook of cannabis*.

Mechoulam, R. (2005). Plant cannabinoids: A neglected pharmacological treasure trove. *British Journal of Pharmacology*, *146*(7), 913–915. http://doi.org/10.1038/sj.bjp.0706415.

Mechoulam, R., Feigenbaum, J. J., Lander, N., Segal, M., Järbe, T. U., Hiltunen, A. J., et al. (1988). Enantiomeric cannabinoids: Stereospecificity of psychotropic activity. *Experientia*, *44*(9), 762–764.

Mechoulam, R., Parker, L. A., & Gallily, R. (2002). Cannabidiol: An overview of some pharmacological aspects. *The Journal of Clinical Pharmacology*, *42*(11 Suppl.), 11S–19S.

Mehmedic, Z., Chandra, S., Slade, D., Denham, H., Foster, S., Patel, A. S., et al. (2010). Potency trends of Δ9-THC and other cannabinoids in confiscated cannabis preparations from 1993 to 2008*. *Journal of Forensic Sciences*, *55*(5), 1209–1217. http://doi.org/10.1111/j.1556-4029.2010.01441.x.

Meier, C., & Mediavilla, V. (1998). Factors influencing the yield and the quality of hemp *(Cannabis sativa* L.) essential oil. *Journal of the International Hemp Association*, *5*(1), 16–20.

Meijer, E. P. M., & Hammond, K. M. (2005). The inheritance of chemical phenotype in Cannabis sativa L. (II): Cannabigerol predominant plants. *Euphytica*, *145*(1–2), 189–198. http://doi.org/10.1007/s10681-005-1164-8.

Meijer, E. P. M., Hammond, K. M., & Micheler, M. (2008). The inheritance of chemical phenotype in Cannabis sativa L. (III): Variation in cannabichromene proportion. *Euphytica*, *165*(2), 293–311. http://doi.org/10.1007/s10681-008-9787-1.

Miller, J. A., Lang, J. E., Ley, M., Nagle, R., Hsu, C. H., Thompson, P. A., et al. (2013). Human breast tissue disposition and bioactivity of limonene in women with early-stage breast cancer. *Cancer Prevention Research (Philadelphia, Pa.)*, *6*(6), 577–584. http://doi.org/10.1158/1940-6207.CAPR-12-0452.

Miyamoto, T., Okimoto, T., & Kuwano, M. (2014). Chemical composition of the essential oil of mastic gum and their antibacterial activity against drug-resistant Helicobacter pylori. *Natural Products and Bioprospecting*, *4*(4), 227–231. http://doi.org/10.1007/s13659-014-0033-3.

Miyazawa, M., & Yamafuji, C. (2005). Inhibition of acetylcholinesterase activity by bicyclic monoterpenoids. *Journal of Agricultural and Food Chemistry*, *53*(5), 1765–1768. http://dx.doi.org/10.1021/jf040019b.

Moghimi, M., Parvardeh, S., Zanjani, T. M., & Ghafghazi, S. (2016). Protective effect of alpha-terpineol against impairment of hippocampal synaptic plasticity and spatial memory following transient cerebral ischemia in rats. *The Iranian Journal of Basic Medical Sciences*, *19*(9), 960–969.

Moldzio, R., Pacher, T., Krewenka, C., Kranner, B., Novak, J., Duvigneau, J. C., et al. (2012). Effects of cannabinoids Δ(9)-tetrahydrocannabinol, Δ(9)-tetrahydrocannabinolic acid and cannabidiol in MPP+ affected murine mesencephalic cultures. *Phytomedicine*, *19*(8–9), 819–824. http://doi.org/10.1016/j.phymed.2012.04.002.

Moreno-Sanz, G. (2016). Can you pass the acid test? Critical review and novel therapeutic perspectives of Δ 9-tetrahydrocannabinolic acid A. *Cannabis and Cannabinoid Research*, *1*(1), 124–130. http://doi.org/10.1089/can.2016.0008.

Moreno-Sanz, G., Duranti, A., Melzig, L., Fiorelli, C., Ruda, G. F., Colombano, G., et al. (2013). Synthesis and structure–activity relationship studies of O-biphenyl-3-yl carbamates as peripherally restricted fatty acid amide hydrolase inhibitors. *Journal of Medicinal Chemistry*, *56*(14), 5917–5930.

Mukerji, G., Yiangou, Y., Corcoran, S. L., Selmer, I. S., Smith, G. D., Benham, C. D., et al. (2006). Cool and menthol receptor TRPM8 in human urinary bladder disorders and clinical correlations. *BMC Urology*, *6*, 6. http://doi.org/10.1186/1471-2490-6-6.

Murillo-Rodriguez, E., Millan-Aldaco, D., Palomero-Rivero, M., Mechoulam, R., & Drucker-Colin, R. (2006). Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. *FEBS Letters*, *580*(18), 4337–4345.

Musty, R. E., & Deyo, R. A. (2006). A cannabigerol extract alters behavioral despair in an animal model of depression. In *Presented at the symposium on the cannabinoids, Tihany* (p. 32). Hungary: International Cannabinoid Research Society.

Musty, R. E., Karniol, I. G., Shirikawa, I., Takahashi, R. N., & Knobel, E. (1976). Interactions of delta-9-tetrahydrocannabinol and cannabinol in man. *The Pharmacology of Marihuana*, *2*, 559–563.

Naef, M., Curatolo, M., Petersen-Felix, S., Arendt-Nielsen, L., Zbinden, A., & Brenneisen, R. (2003). The analgesic effect of oral delta-9-tetrahydrocannabinol (THC), morphine, and a THC-morphine combination in healthy subjects under experimental pain conditions. *Pain*, *105*(1–2), 79–88.

Name Withheld. (2006). Studying the effects of terpenes. *O'Shaughnessy's* (Spring 2006), 2.

Neff, G. W., O'Brien, C. B., Reddy, K. R., Bergasa, N. V., Regev, A., Molina, E., et al. (2002). Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *The American Journal of Gastroenterology*, *97*(8), 2117–2119.

Nicholson, A. N., Turner, C., Stone, B. M., & Robson, P. J. (2004). Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *Journal of Clinical Psychopharmacology*, *24*(3), 305–313.

Nogueira, M. N., Aquino, S. G., Rossa Junior, C., & Spolidorio, D. M. (2014). Terpinen-4-ol and alpha-terpineol (tea tree oil components) inhibit the production of IL-1beta, IL-6 and IL-10 on human macrophages. *Inflammation Research*, *63*(9), 769–778. http://doi.org/10.1007/s00011-014-0749-x.

Noma, Y., & Asakawa, Y. (2010). Biotransformation of monoterpenoids by microorganisms, insects, and mammals. In K. H. C. Baser & G. Buchbauer (Eds.), *Handbook of essential oils: Science, technology, and applications* (pp. 585–736). Boca Raton, FL: CRC Press.

Noskova, K., Dovrtelova, G., Zendulka, O., Řemínek, R., & Jurica, J. (2016). The effect of (-)-linalool on the metabolic activity of liver CYP enzymes in rats. *Physiological Research/Academia Scientiarum Bohemoslovaca*, *65*(Suppl. 4), S499–S504.

Okumura, N., Yoshida, H., Nishimura, Y., Kitagishi, Y., & Matsuda, S. (2012). Terpinolene, a component of herbal sage, downregulates AKT1 expression in K562 cells. *Oncology Letters*, *3*(2), 321–324. http://doi.org/10.3892/ol.2011.491.

Onaivi, E. S., Ishiguro, H., Gong, J.-P., Patel, S., Meozzi, P. A., Myers, L., et al. (2008). Brain neuronal CB2 cannabinoid receptors in drug abuse and depression: From mice to human subjects. *PloS One*, *3*(2), e1640. http://doi.org/10.1371/journal.pone.0001640.

Onawunmi, G. O., Yisak, W. A., & Ogunlana, E. O. (1984). Antibacterial constituents in the essential oil of Cymbopogon citratus (DC.) Stapf. *Journal of Ethnopharmacology*, *12*(3), 279–286.

Opdyke, D. L. J. (1983). Caryophyllene oxide. *Food and Chemical Toxicology*, *21*(5), 661–662.

Pacher, P. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological Reviews*, *58*(3), 389–462. http://doi.org/10.1124/pr.58.3.2.

Pacher, P., & Mechoulam, R. (2011). Is lipid signaling through cannabinoid 2 receptors part of a protective system? *Progress in Lipid Research*, *50*(2), 193–211. http://doi.org/10.1016/j.plipres.2011.01.001.

Park, H. M., Lee, J. H., Yaoyao, J., Jun, H. J., & Lee, S. J. (2011). Limonene, a natural cyclic terpene, is an agonistic ligand for adenosine A(2A) receptors. *Biochemical and Biophysical Research Communications*, *404*(1), 345–348. http://doi.org/10.1016/j.bbrc.2010.11.121.

Parker, L. A. (2003). Taste avoidance and taste aversion: Evidence for two different processes. *Animal Learning & Behavior*, *31*(2), 165–172.

Parvardeh, S., Moghimi, M., Eslami, P., & Masoudi, A. (2016). Alpha-Terpineol attenuates morphine-induced physical dependence and tolerance in mice: Role of nitric oxide. *The Iranian Journal of Basic Medical Sciences*, *19*(2), 201–208.

Paula-Freire, L. I., Andersen, M. L., Gama, V. S., Molska, G. R., & Carlini, E. L. (2014). The oral administration of trans-caryophyllene attenuates acute and chronic pain in mice. *Phytomedicine*, *21*(3), 356–362. http://doi.org/10.1016/j.phymed.2013.08.006.

Peana, A. T., Rubattu, P., Piga, G. G., Fumagalli, S., Boatto, G., Pippia, P., et al. (2006). Involvement of adenosine A1 and A2A receptors in (-)-linalool-induced antinociception. *Life Sciences*, *78*(21), 2471–2474. http://doi.org/10.1016/j.lfs.2005.10.025.

Peng, X., Zhao, Y., Liang, X., Wu, L., Cui, S., Guo, A., et al. (2006). Assessing the quality of RCTs on the effect of beta-elemene, one ingredient of a Chinese herb, against malignant tumors. *Contemporary Clinical Trials*, *27*(1), 70–82. http://doi.org/10.1016/j.cct.2005.07.002.

Perry, N. S., Houghton, P. J., Theobald, A., Jenner, P., & Perry, E. K. (2000). In-vitro inhibition of human erythrocyte acetylcholinesterase by salvia lavandulaefolia essential oil and constituent terpenes. *Journal of Pharmacy and Pharmacology*, *52*(7), 895–902.

Pertwee, R. G. (1988). The central neuropharmcology of psychotropic cannabinoids. *Pharmacology and Therapeutics*, *36*(2–3), 189–261. http://doi.org/10.1016/0163-7258(88)90106-4.

Pertwee, R. G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *British Journal of Pharmacology*, *153*(2), 199–215. http://doi.org/10.1038/sj.bjp.0707442.

Pertwee, R. G., & Cascio, M. G. (2014). Known pharmacological actions of delta-9-tetrahydrocannabinol and of four other chemical constituents of cannabis that activate cannabinoid receptors. In R. G. Pertwee (Ed.), *Handbook of cannabis* (pp. 115–136). Oxford, UK: Oxford University Press. http://doi.org/10.1093/acprof:oso/9780199662685.003.0006.

Pertwee, R. G., Howlett, A. C., Abood, M. E., Alexander, S. P. H., Di Marzo, V., Elphick, M. R., et al. (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB_1 and CB_2. *Pharmacological Reviews*, *62*(4), 588–631. http://doi.org/10.1124/pr.110.003004.

Piccinelli, A. C., Morato, P. N., Dos Santos Barbosa, M., Croda, J., Sampson, J., Kong, X., et al. (2017). Limonene reduces hyperalgesia induced by gp120 and cytokines by modulation of IL-1 beta and protein expression in spinal cord of mice. *Life Sciences*, *174*, 28–34. http://doi.org/10.1016/j.lfs.2016.11.017.

Piccinelli, A. C., Santos, J. A., Konkiewitz, E. C., Oesterreich, S. A., Formagio, A. S., Croda, J., et al. (2015). Antihyperalgesic and antidepressive actions of (R)-(+)-limonene, alpha-phellandrene, and essential oil from Schinus terebinthifolius fruits in a neuropathic pain model. *Nutritional Neuroscience*, *18*(5), 217–224. http://doi.org/10.1179/1476830514Y.0000000119.

Plengsuriyakarn, T., Karbwang, J., & Na-Bangchang, K. (2015). Anticancer activity using positron emission tomography-computed tomography and pharmacokinetics of beta-eudesmol in human cholangiocarcinoma xenografted nude mouse model. *Clinical and Experimental Pharmacology and Physiology*, *42*(3), 293–304. http://doi.org/10.1111/1440-1681.12354.

Potter, D. J. (2009). *The propagation, characterisation and optimisation of Cannabis sativa L. as a phytopharmaceutical. Pharmaceutical Sciences* (p.224). London: King's College.

Pultrini Ade, M., Galindo, L. A., & Costa, M. (2006). Effects of the essential oil from Citrus aurantium L. in experimental anxiety models in mice. *Life Sciences*, *78*(15), 1720–1725. http://doi.org/10.1016/j.lfs.2005.08.004.

Qin, N., Neeper, M. P., Liu, Y., Hutchinson, T. L., Lubin, M. L., & Flores, C. M. (2008). TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(24), 6231–6238. http://dx.doi.org/10.1523/JNEUROSCI.0504-08.2008.28/24/6231 [pii].

Quintans-Junior, L., Moreira, J. C., Pasquali, M. A., Rabie, S. M., Pires, A. S., Schroder, R., et al. (2013). Antinociceptive activity and redox profile of the monoterpenes (+)-camphene, p-cymene, and geranyl acetate in experimental models. *ISRN Toxicology*, *2013*, 459530. http://doi.org/10.1155/2013/459530.

Quintans-Junior, L. J., Oliveira, M. G., Santana, M. F., Santana, M. T., Guimaraes, A. G., Siqueira, J. S., et al. (2011). Alpha-terpineol reduces nociceptive behavior in mice. *Pharmaceutical Biology*, *49*(6), 583–586. http://doi.org/10.3109/13880209.2010.529616.

Ramalho, T. R., Pacheco de Oliveira, M. T., Lima, A. L., Bezerra-Santos, C. R., & Piuvezam, M. R. (2015). Gamma-terpinene modulates acute inflammatory response in mice. *Planta Medica*, *81*(14), 1248–1254. http://doi.org/10.1055/s-0035-1557790.

Raman, A., Weir, U., & Bloomfield, S. F. (1995). Antimicrobial effects of tea-tree oil and its major components on Staphylococcus aureus, Staph. epidermidis and Propionibacterium acnes. *Letters in Applied Microbiology*, *21*(4), 242–245.

Rao, V. S., Menezes, A. M., & Viana, G. S. (1990). Effect of myrcene on nociception in mice. *The Journal of Pharmacy and Pharmacology*, *42*(12), 877–878.

Re, L., Barocci, S., Sonnino, S., Mencarelli, A., Vivani, C., Paolucci, G., et al. (2000). Linalool modifies the nicotinic receptor–ion channel kinetics at the mouse neuromuscular junction. *Pharmacological Research*, *42*(2), 177–181. http://doi.org/10.1006/phrs.2000.0671.

Reagan-Shaw, S., Nihal, M., & Ahmad, N. (2008). Dose translation from animal to human studies revisited. *The FASEB Journal*, *22*(3), 659–661. http://doi.org/10.1096/fj.07-9574LSF.

Rhee, Man-Hee, Vogel, Zvi, Barg, Jacob, Bayewitch, Michael, Levy, Rivka, Hanuš, Lumir, et al. (1997). Cannabinol derivatives: Binding to cannabinoid receptors and inhibition of adenylylcyclase. *Journal of Medicinal Chemistry*, *40*(20), 3228–3233. http://doi.org/10.1021/jm970126f.

Riedel, G., Fadda, P., McKillop-Smith, S., Pertwee, R. G., Platt, B., & Robinson, L. (2009). Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. *British Journal of Pharmacology*, *156*(7), 1154–1166. http://doi.org/10.1111/j.1476-5381.2008.00107.x.

Rivas da Silva, A. C., Lopes, P. M., Barros de Azevedo, M. M., Costa, D. C., Alviano, C. S., & Alviano, D. S. (2012). Biological activities of alpha-pinene and beta-pinene enantiomers. *Molecules (Basel, Switzerland)*, *17*(6), 6305–6316. http://doi.org/10.3390/molecules17066305.

Robson, P. (2011). Abuse potential and psychoactive effects of delta-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine. *Expert Opinion on Drug Safety*, *10*(5), 675–685. http://dx.doi.org/10.1517/14740338.2011.575778.

Rock, E. M., Kopstick, R. L., Limebeer, C. L., & Parker, L. A. (2013). Tetrahydrocannabinolic acid reduces nausea-induced conditioned gaping in rats and vomiting in Suncus murinus. *British Journal of Pharmacology*, *170*(3), 641–648. http://doi.org/10.1111/bph.12316.

Rock, E. M., & Parker, L. A. (2015). Synergy between cannabidiol, cannabidiolic acid, and Δ^9-tetrahydrocannabinol in the regulation of emesis in the Suncus murinus (house musk shrew). *Behavioral Neuroscience*, *129*(3), 368–370. http://doi.org/10.1037/bne0000057.

Rock, E. M., Sticht, M. A., & Parker, L. A. (2014). Effect of phytocannabinoids on nausea and vomiting. In R. G. Pertwee (Ed.), *Handbook of cannabis* (pp. 435–454). Oxford, UK: Oxford University Press. http://doi.org/10.1093/acprof:oso/9780199662685.003.0023.

Rodrigues Goulart, H., Kimura, E. A., Peres, V. J., Couto, A. S., Aquino Duarte, F. A., & Katzin, A. M. (2004). Terpenes arrest parasite development and inhibit biosynthesis of isoprenoids in Plasmodium falciparum. *Antimicrobial Agents and Chemotherapy*, *48*(7), 2502–2509.

Rodrigues, K. A., Amorim, L. V., Dias, C. N., Moraes, D. F., Carneiro, S. M., & Carvalho, F. A. (2015). Syzygium cumini (L.) Skeels essential oil and its major constituent alpha-pinene exhibit anti-Leishmania activity through immunomodulation in vitro. *Journal of Ethnopharmacology*, *160*, 32–40. http://doi.org/10.1016/j.jep.2014.11.024.

Rog, D. J., Nurmiko, T., Friede, T., & Young, C. (2005). Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. *Neurology*, *65*(6), 812–819.

Romano, B., Borrelli, F., Fasolino, I., Capasso, R., Piscitelli, F., Cascio, M., et al. (2013). The cannabinoid TRPA1 agonist cannabichromene inhibits nitric oxide production in macrophages and ameliorates murine colitis. *British Journal of Pharmacology*, *169*(1), 213–229. http://doi.org/10.1111/bph.12120.

Rosenthaler, S., Pöhn, B., Kolmanz, C., Huu, C. N., Krewenka, C., Huber, A., et al. (2014). Differences in receptor binding affinity of several phytocannabinoids do not explain their effects on neural cell cultures. *Neurotoxicology and Teratology*, *46*, 49–56. http://doi.org/10.1016/j.ntt.2014.09.003.

Rufino, A. T., Ribeiro, M., Sousa, C., Judas, F., Salgueiro, L., Cavaleiro, C., et al. (2015). Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis. *European Journal of Pharmacology*, *750*, 141–150. http://doi.org/10.1016/j.ejphar.2015.01.018.

Russo, E. B. (2001). *Handbook of psychotropic herbs: A scientific analysis of herbal remedies for psychiatric conditions*. Binghamton, NY: Haworth Press.

Russo, E. B. (2007). History of cannabis and its preparations in saga, science, and sobriquet. *Chemistry & Biodiversity*, *4*(8), 1614–1648.

Russo, E. B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology*, *163*(7), 1344–1364. http://doi.org/10.1111/j.1476-5381.2011.01238.x.

Russo, E. B. (2013). *Cannabis strains: Do cannabis strains differ?* Retrieved January 18, 2017, from http://www.cannabis-med.org/index.php?tpl=faq&red=faqlist&id=278&lng=en.

Russo, E. B. (2014). The pharmacological history of Cannabis. In R. Pertwee (Ed.), *Handbook of Cannabinoids*. (pp. 23–43). Oxford, United Kingdom: Oxford University Press.

Russo, E. B. (2016a). Beyond cannabis: Plants and the endocannabinoid system. *Trends in Pharmacological Sciences*, *37*(7), 594–605. http://dx.doi.org/10.1016/j.tips.2016.04.005.

Russo, E. B. (2016b). Cannabis and epilepsy: An ancient treatment returns to the fore. *Epilepsy and Behavior*. http://dx.doi.org/10.1016/j.yebeh.2016.09.040.

Russo, E. B. (2017). Cannabis and epilepsy: An ancient treatment returns to the fore. *Epilepsy Behav*, *70*(Pt B), 292–297. http://dx.doi.org/10.1016/j.yebeh.2016.09.040.

Russo, E. B., Burnett, A., Hall, B., & Parker, K. K. (2005). Agonistic properties of cannabidiol at 5-HT-1a receptors. *Neurochemical Research*, *30*(8), 1037–1043.

Russo, E. B., & Guy, G. W. (2006). A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Medical Hypotheses*, *66*(2), 234–246. http://dx.doi.org/10.1016/j.mehy.2005.08.026.

Russo, E. B., Guy, G. W., & Robson, P. J. (2007). Cannabis, pain, and sleep: Lessons from therapeutic clinical trials of Sativex, a cannabis-based medicine. *Chemistry & Biodiversity*, *4*(8), 1729–1743. http://doi.org/10.1002/cbdv.200790150.

Russo, E. B., & Hohmann, A. G. (2012). *Role of cannabinoids in pain management. In Comprehensive treatment of chronic pain by medical, interventional, and integrative approaches* (pp. 181–197). New York, NY: Springer New York. http://doi.org/10.1007/978-1-4614-1560-2_18.

Sastre-Garriga, J., Vila, C., Clissold, S., & Montalban, X. (2011). THC and CBD oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis. *Expert Review of Neurotherapeutics*, *11*(5), 627–637. http://dx.doi.org/10.1586/ern.11.47.

Sanguinetti, M., Posteraro, B., Romano, L., Battaglia, F., Lopizzo, T., De Carolis, E., et al. (2007). In vitro activity of Citrus bergamia (bergamot) oil against clinical isolates of dermatophytes. *The Journal of Antimicrobial Chemotherapy*, *59*(2), 305–308. http://doi.org/10.1093/jac/dkl473.

Satou, T., Kasuya, H., Maeda, K., & Koike, K. (2014). Daily inhalation of alpha-pinene in mice: Effects on behavior and organ accumulation. *Phytotherapy Research*, *28*(9), 1284–1287.

Sayyah, M., Nadjafnia, L., & Kamalinejad, M. (2004). Anticonvulsant activity and chemical composition of Artemisia dracunculus L. essential oil. *Journal of Ethnopharmacology*, *94*(2–3), 283–287.

Scuderi, C., De Filippis, D., Iuvone, T., Blasio, A., Steardo, A., & Esposito, G. (2009). Cannabidiol in medicine: A review of its therapeutic potential in CNS disorders. *Phytotherapy Research*, *23*(5), 597–602. http://doi.org/10.1002/ptr.2625.

Schafer, D., & Schafer, W. (1981). Pharmacological studies with an ointment containing menthol, camphene and essential oils for broncholytic and secretolytic effects. *Arzneimittel-Forschung*, *31*(1), 82–86.

Schmidt, L., Belov, V. N., & Goen, T. (2015). Human metabolism of Delta3-carene and renal elimination of Delta3-caren-10-carboxylic acid (chaminic acid) after oral administration. *Archives of Toxicology*, *89*(3), 381–392. http://doi.org/10.1007/s00204-014-1251-5.

Schnaubelt, K. (1998). *Advanced aromatherapy: The science of essential oil therapy* (1st ed.). Rochester, VT: Healing Arts Press.

Schott, M., Klein, B., & Vilcinskas, A. (2015). Detection of illicit drugs by trained honeybees (Apis mellifera). *PloS One*, *10*(6), e0128528. http://doi.org/10.1371/journal.pone.0128528.

Scutt, A., & Williamson, E. M. (2007). Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors. *Calcified Tissue International*, *80*(1), 50–59. http://doi.org/10.1007/s00223-006-0171-7.

Sellers, E. M., Schoedel, K., Bartlett, C., Romach, M., Russo, E. B., Stott, C. G., et al. (2013). A multiple-dose, randomized, double-blind, placebo-controlled, parallel-group QT/QTc study to evaluate the electrophysiologic effects of THC/CBD spray. *Clinical Pharmacology in Drug Development*, *2*(3), 285–294. http://doi.org/10.1002/cpdd.36.

Semenya, S., Potgieter, M., Tshisikhawe, M., Shava, S., & Maroyi, A. (2012). Medicinal utilization of exotic plants by Bapedi traditional healers to treat human ailments in Limpopo province, South Africa. *Journal of Ethnopharmacology*, *144*(3), 646–655. http://doi.org/10.1016/j.jep.2012.10.005.

Sharma, C., Al Kaabi, J. M., Nurulain, S. M., Goyal, S. N., Kamal, M. A., & Ojha, S. (2016). Polypharmacological properties and therapeutic potential of β-caryophyllene: A dietary phytocannabinoid of pharmaceutical promise. *Current Pharmaceutical Design*, *22*(21), 3237–3264.

Shelly, T. E., & Nishimoto, J. I. (2015). Exposure to the plant compound {alpha} -humulene reduces mating success in male Mediterranean fruit flies (Diptera: Tephritidae). *Annals of the Entomological Society of America*, *108*(3), 215–221. http://doi.org/10.1093/aesa/sav008.

Shinjyo, N., & Di Marzo, V. (2013). The effect of cannabichromene on adult neural stem/progenitor cells. *Neurochemistry International*, *63*(5), 432–437. http://doi.org/10.1016/j.neuint.2013.08.002.

Shoyama, Y., Hirano, H., Makino, H., Umekita, N., & Nishioka, I. (1977). Cannabis. X. The isolation and structures of four new propyl cannabinoid acids, tetrahydrocannabivarinic acid, cannabidivarinic acid, cannabichromevarinic acid and cannabigerovarinic acid, from Thai Cannabis, 'Meao variant'. *Chemical & Pharmaceutical Bulletin*, *25*(9), 2306–2311. http://doi.org/10.1248/cpb.25.2306.

Silva Brum, L. F., Emanuelli, T., Souza, D. O., & Elisabetsky, E. (2001). Effects of linalool on glutamate release and uptake in mouse cortical synaptosomes. *Neurochemical Research*, *26*(3), 191–194.

Singh, P., Shukla, R., Prakash, B., Kumar, A., Singh, S., Mishra, P. K., et al. (2010). Chemical profile, antifungal, antiaflatoxigenic and antioxidant activity of Citrus maxima Burm. and Citrus sinensis (L.) Osbeck essential oils and their cyclic monoterpene, DL-limonene. *Food and Chemical Toxicology*, *48*(6), 1734–1740. http://doi.org/10.1016/j.fct.2010.04.001.

Siqueira, H. D., Neto, B. S., Sousa, D. P., Gomes, B. S., da Silva, F. V., Cunha, F. V., et al. (2016). alpha-Phellandrene, a cyclic monoterpene, attenuates inflammatory response through neutrophil migration inhibition and mast cell degranulation. *Life Sciences*, *160*, 27–33. http://doi.org/10.1016/j.lfs.2016.07.008.

Sirikantaramas, S., Morimoto, S., Shoyama, Y., Ishikawa, Y., Wada, Y., Shoyama, Y., et al. (2004). The gene controlling marijuana psychoactivity: Molecular cloning and heterologous expression of delta1-tetrahydrocannabinolic acid synthase from Cannabis sativa L. *The Journal of Biological Chemistry*, *279*(38), 39767–39774.

Slatkin, D. J., Doorenbos, N. J., Harris, L. S., Masoud, A. N., Quimby, M. W., & Schiff, P. L. J. (1971). Chemical constituents of Cannabis sativa L. root. *Journal of Pharmaceutical Sciences*, *60*(12), 1891–1892.

Slatkin, D. J., Knapp, J. E., Schiff, P. L. J., Turner, C. E., & Mole, L. M. J. (1975). Steroids of Cannabis sativa root. *Phytochemistry*, *14*, 580–581.

Soni, D., Smoum, R., Breuer, A., Mechoulam, R., & Steinberg, D. (2015). Effect of the synthetic cannabinoid HU-210 on quorum sensing and on the production of quorum sensing-mediated virulence factors by Vibrio harveyi. *BMC Microbiology*, *15*, 159. http://doi.org/10.1186/s12866-015-0499-0.

Stahl, E., & Kunde, R. (1973). Die Leitsubstanzen der Haschisch-Suchhunde. *Kriminalistik: Zeitschrift Für Die Gesamte Kriminalistische Wissenschaft Und Praxis*, *27*(9), 385–389.

Stott, C. G., Guy, G. W., Wright, S., & Whittle, B. A. (2005). The effects of cannabis extracts Tetranabinex and Nabidiolex on human cytochrome P450-mediated metabolism. In *Presented at the symposium on the cannabinoids* (p. 163). Clearwater, FL: International Cannabinoid Research Association.

Subramenium, G. A., Vijayakumar, K., & Pandian, S. K. (2015). Limonene inhibits streptococcal biofilm formation by targeting surface-associated virulence factors. *Journal of Medical Microbiology*, *64*(8), 879–890. http://doi.org/10.1099/jmm.0.000105.

Sulak, D., Saneto, R., & Goldstein, B. (2017). The current status of artisanal cannabis for the treatment of epilepsy in the United States. *Epilepsy Behav*, *70*(Pt B), 328–333. http://dx.doi.org/10.1016/j.yebeh.2016.12.032.

Sunil, C., Duraipandiyan, V., Ignacimuthu, S., & Al-Dhabi, N. A. (2013). Antioxidant, free radical scavenging and liver protective effects of friedelin isolated from Azima tetracantha Lam. leaves. *Food Chemistry*, *139*(1–4), 860–865. http://doi.org/10.1016/j.foodchem.2012.12.041.

Swift, W., Wong, A., Li, K. M., Arnold, J. C., & McGregor, I. S. (2013). Analysis of cannabis seizures in NSW, Australia: Cannabis potency and cannabinoid profile. *PloS One*, *8*(7), e70052. http://doi.org/10.1371/journal.pone.0070052.

Takeda, S., Misawa, K., Yamamoto, I., & Watanabe, K. (2008). Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. *Drug Metabolism and Disposition*, *36*(9), 1917–1921. http://doi.org/10.1124/dmd.108.020909.

Takemoto, H., Ito, M., Shiraki, T., Yagura, T., & Honda, G. (2008). Sedative effects of vapor inhalation of agarwood oil and spikenard extract and identification of their active components. *Journal of Natural Medicines*, *62*(1), 41–46. http://doi.org/10.1007/s11418-007-0177-0.

Tambe, Y., Tsujiuchi, H., Honda, G., Ikeshiro, Y., & Tanaka, S. (1996). Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, beta-caryophyllene. *Planta Medica*, *62*(5), 469–470.

Thomas, A., Baillie, G. L., Phillips, A. M., Razdan, R. K., Ross, R. A., & Pertwee, R. G. (2007). Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *British Journal of Pharmacology*, *150*(5), 613–623. http://doi.org/10.1038/sj.bjp.0707133.

Tisserand, R., & Young, R. (2014). *Essential oil safety* (2nd ed.). Edinburgh, UK: Churchill Livingstone Elsevier.

Torres, S., Lorente, M., Rodriguez-Fornes, F., Hernandez-Tiedra, S., Salazar, M., Garcia-Taboada, E., et al. (2011). A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Molecular Cancer Therapeutics*, *10*(1), 90–103. http://doi.org/10.1158/1535-7163.MCT-10-0688.

Turkez, H., Aydin, E., Geyikoglu, F., & Cetin, D. (2015). Genotoxic and oxidative damage potentials in human lymphocytes after exposure to terpinolene in vitro. *Cytotechnology*, *67*(3), 409–418. http://doi.org/10.1007/s10616-014-9698-z.

Turkez, H., Sozio, P., Geyikoglu, F., Tatar, A., Hacimuftuoglu, A., & Di Stefano, A. (2014). Neuroprotective effects of farnesene against hydrogen peroxide-induced neurotoxicity in vitro. *Cellular and Molecular Neurobiology*, *34*(1), 101–111. http://doi.org/10.1007/s10571-013-9991-y.

Turner, C. E., Elsohly, M. A., & Boeren, E. G. (1980). Constituents of Cannabis sativa L. XVII. A review of the natural constituents. *Journal of Natural Products*, *43*(2), 169–234.

Turner, C. E., Hsu, M. H., Knapp, J. E., Schiff, P. L. J., & Slatkin, D. J. (1976). Isolation of cannabisativine, an alkaloid, from Cannabis sativa L. root. *Journal of Pharmaceutical Sciences*, *65*(7), 1084–1085.

Upton, R., Craker, L., ElSohly, M., Romm, A., Russo, E., & Sexton, M. (2013). Cannabis inflorescence: Cannabis spp.: Standards of identity, analysis and quality control. In R. Upton (Ed.), Scotts Valley, CA, USA: American Herbal Pharmacopoeia.

Vallianou, I., & Hadzopoulou-Cladaras, M. (2016). Camphene, a plant derived monoterpene, exerts its hypolipidemic action by affecting SREBP-1 and MTP expression. *PloS One*, *11*(1), e0147117. http://doi.org/10.1371/journal.pone.0147117.

Vallianou, I., Peroulis, N., Pantazis, P., & Hadzopoulou-Cladaras, M. (2011). Camphene, a plant-derived monoterpene, reduces plasma cholesterol and triglycerides in hyperlipidemic rats independently of HMG-CoA reductase activity. *PloS One*, *6*(11), e20516. http://doi.org/10.1371/journal.pone.0020516.

Varga, Z. V., Matyas, C., Erdelyi, K., Cinar, R., Nieri, D., Chicca, A., et al. (2017). Beta-caryophyllene protects against alcoholic steatohepatitis by attenuating inflammation and metabolic dysregulation in mice. *British Journal of Pharmacology*. http://dx.doi.org/10.1111/bph.13722.

Verhoeckx, K. C., Korthout, H. A., van Meeteren-Kreikamp, A. P., Ehlert, K. A., Wang, M., van der Greef, J., et al. (2006). Unheated Cannabis sativa extracts and its major compound THC-acid have potential immuno-modulating properties not mediated by CB1 and CB2 receptor coupled pathways. *International Immunopharmacology*, *6*(4), 656–665. http://doi.org/10.1016/j.intimp.2005.10.002.

Vigushin, D. M., Poon, G. K., Boddy, A., English, J., Halbert, G. W., Pagonis, C., et al. (1998). Phase I and pharmacokinetic study of D-limonene in patients with advanced cancer. Cancer Research Campaign Phase I/II Clinical Trials Committee. *Cancer Chemotherapy and Pharmacology*, *42*(2), 111–117.

Volicer, L., Stelly, M., Morris, J., McLaughlin, J., & Volicer, B. J. (1997). Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *12*(9), 913–919.

Von Burg, R. (1995). Toxicology update. Limonene. *Journal of Applied Toxicology*, *15*(6), 495–499.

Wattenberg, L. W. (1991). Inhibition of azoxymethane-induced neoplasia of the large bowel by 3-hydroxy-3,7,11-trimethyl-1,6,10-dodecatriene (nerolidol). *Carcinogenesis*, *12*(1), 151–152.

Wade, D. T., Collin, C., Stott, C., & Duncombe, P. (2010). Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. *Multiple Sclerosis*, *16*(6), 707–714. http://dx.doi.org/10.1177/1352458510367462, 16/6/707 [pii].

Werz, O., Seegers, J., Schaible, A. M., Weinigel, C., Barz, D., Koeberle, A., et al. (2014). Cannflavins from hemp sprouts, a novel cannabinoid-free hemp food product, target microsomal prostaglandin E2 synthase-1 and 5-lipoxygenase. *Pharma Nutrition*, *2*(3), 53–60. http://doi.org/10.1016/j.phanu.2014.05.001.

Wilkinson, J. D., & Williamson, E. M. (2007). Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *Journal of Dermatological Science*, *45*(2), 87–92.

Williams, S. J., Hartley, J. P., & Graham, J. D. (1976). Bronchodilator effect of delta1-tetrahydrocannabinol administered by aerosol of asthmatic patients. *Thorax*, *31*(6), 720–723.

Williams, C. M., Jones, N. A., & Whalley, B. J. (2014). *Cannabis and epilepsy*. *In Handbook of cannabis* (pp. 547–563). Oxford, UK: Oxford University Press. http://doi.org/10.1093/acprof:oso/9780199662685.003.0030.

Wood, T. B., Spivey, W. T. N., & Easterfield, T. H. (1899). III.—Cannabinol. Part I. *Journal of the Chemical Society, Transactions*, *75*, 20–36. http://doi.org/10.1039/CT8997500020.

Wu, L., Wang, G., Tang, S., Long, G., & Yin, T. (2011). Protection of endothelial cells, inhibition of neointimal hyperplasia by beta-elemene in an injured artery. *Cardiovascular Drugs and Therapy*, *25*(3), 233–242. http://doi.org/10.1007/s10557-011-6305-9.

Wu, X. S., Xie, T., Lin, J., Fan, H. Z., Huang-Fu, H. J., Ni, L. F., et al. (2009). An investigation of the ability of elemene to pass through the blood-brain barrier and its effect on brain carcinomas. *Journal of Pharmacy and Pharmacology*, *61*(12), 1653–1656. http://doi.org/10.1211/jpp/61.12.0010.

Xi, Z.-X., Peng, X.-Q., Li, X., Song, R., Zhang, H.-Y., Liu, Q.-R., et al. (2011). Brain cannabinoid CB2 receptors modulate cocaine's actions in mice. *Nature Neuroscience*, *14*(9), 1160–1166. http://doi.org/10.1038/nn.2874.

Xu, H. B., Zheng, L. P., Li, L., Xu, L. Z., & Fu, J. (2013). Elemene, one ingredient of a Chinese herb, against malignant tumors: A literature-based meta-analysis. *Cancer Investigation*, *31*(2), 156–166. http://doi.org/10.3109/07357907.2012.756108.

Yamaori, S., Koeda, K., Kushihara, M., Hada, Y., Yamamoto, I., & Watanabe, K. (2012). Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity. *Drug Metabolism and Pharmacokinetics*, *27*(3), 294–300. http://doi.org/10.2133/dmpk.DMPK-11-RG-107.

Yamaori, S., Kushihara, M., Yamamoto, I., & Watanabe, K. (2010). Characterization of major phytocannabinoids, cannabidiol and cannabinol, as isoform-selective and potent inhibitors of human CYP1 enzymes. *Biochemical Pharmacology*, *79*(11), 1691–1698. http://doi.org/10.1016/j.bcp.2010.01.028.

Yamaori, S., Okamoto, Y., Yamamoto, I., & Watanabe, K. (2011). Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6. *Drug Metabolism and Disposition*, *39*(11), 2049–2056. http://doi.org/10.1124/dmd.111.041384.

Yang, D., Michel, L., Chaumont, J. P., & Millet-Clerc, J. (1999). Use of caryophyllene oxide as an antifungal agent in an in vitro experimental model of onychomycosis. *Mycopathologia*, *148*(2), 79–82.

Yang, H. H., Son, J. K., Jung, B., Zheng, M., & Kim, J. R. (2011). Epifriedelanol from the root bark of Ulmus davidiana inhibits cellular senescence in human primary cells. *Planta Medica*, 77(5), 441–449. http://doi.org/10.1055/s-0030-1250458.

Yang, Q., Wu, J., Luo, Y., Huang, N., Zhen, N., Zhou, Y., et al. (2016). (-)-Guaiol regulates RAD51 stability via autophagy to induce cell apoptosis in non-small cell lung cancer. *Oncotarget*, 7(38), 62585–62597. http://doi.org/10.18632/oncotarget.11540.

Yeshurun, M., Shpilberg, O., Herscovici, C., Shargian, L., Dreyer, J., Peck, A., et al. (2015). Cannabidiol for the prevention of graft-versus-host-disease after allogeneic hematopoietic cell transplantation: Results of a phase II study. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*, *21*(10), 1770–1775. http://doi.org/10.1016/j.bbmt.2015.05.018.

Zanoli, P., & Zavatti, M. (2008). Pharmacognostic and pharmacological profile of Humulus lupulus L. *Journal of Ethnopharmacology*, *116*(3), 383–396. http://doi.org/10.1016/j.jep.2008.01.011.

Zhang, J., Zhang, H. D., Yao, Y. F., Zhong, S. L., Zhao, J. H., & Tang, J. H. (2015). beta-elemene reverses chemoresistance of breast cancer cells by reducing resistance transmission via exosomes. *Cellular Physiology and Biochemistry*, *36*(6), 2274–2286. http://doi.org/10.1159/000430191.

Zhou, Y. Y., Liu, H. X., Jiang, N., Feng, X. H., Feng, X. Y., Zhang, H. Q., et al. (2015). Elemene, the essential oil of Curcuma wenyujin, inhibits osteogenic differentiation in ankylosing spondylitis. *Joint, Bone, Spine*, *82*(2), 100–103. http://doi.org/10.1016/j.jbspin.2014.05.004.

Zhu, T., Li, X., Luo, L., Wang, X., Li, Z., Xie, P., et al. (2015). Reversion of malignant phenotypes of human glioblastoma cells by beta-elemene through beta-catenin-mediated regulation of stemness-, differentiation- and epithelial-to-mesenchymal transition-related molecules. *Journal of Translational Medicine*, *13*, 356. http://doi.org/10.1186/s12967-015-0727-2.

Zou, K., Liu, C., Zhang, Z., & Zou, L. (2015). The effect of elemene on lung adenocarcinoma A549 cell radiosensitivity and elucidation of its mechanism. *Clinics (São Paulo, Brazil)*, *70*(8), 556–562. http://doi.org/10.6061/clinics/2015(08)05.

Zou, S., Wang, C., Cui, Z., Guo, P., Meng, Q., Shi, X., et al. (2016). Beta-elemene induces apoptosis of human rheumatoid arthritis fibroblast-like synoviocytes via reactive oxygen species-dependent activation of p38 mitogen-activated protein kinase. *Pharmacological Reports*, *68*(1), 7–11. http://doi.org/10.1016/j.pharep.2015.06.004.

Clinical Social Work Journal
https://doi.org/10.1007/s10615-018-0670-9

ORIGINAL PAPER

Medical Cannabis in Adult Mental Health Settings: Reconstructing One of the Most Maligned Medications in the United States

Jan Roberts[1]

Abstract
Although twenty-nine states in the United States of America have legalized medical cannabis, the stigma surrounding cannabis continues and few clinicians have been educated on its use and benefits. This paper presents the history of therapeutic cannabis use as well as the political perspectives and federal laws leading to ongoing stigmatization of this substance and its users. A summary of cannabis' therapeutic properties, and its potential use in the treatment of mental health problems is discussed.

Keywords Cannabis · Marijuana · Mental health · Endocannabinoid system · Medical cannabis · Medical marijuana · Gateway drug · US drug policy

Introduction

Prior to 1937 cannabis was legal in the United States (Moeller and Woods 2015). Until that time, cannabis was widely acknowledged to be in the pantheon for medicinal purposes (Moeller and Woods 2015). In 1970, The United States Controlled Substance Act identified cannabis, colloquially known as marijuana, as one of the most dangerous drugs, comparable to heroin and LSD (Drug Enforcement Agency 2017). As a result, US policy has created an environment making it practically prohibitive to conduct research on cannabis and its effects on physical and mental health (National Academies 2017). Despite federal law, medical cannabis is currently legal in 29 states and the District of Columbia (29 legal medical marijuana states and DC 2017). Admittedly, there is a potential for cannabis abuse as there is for alcohol, food, and other prescribed and non-prescribed substances. However, current international research supports the beneficial use of cannabis for the treatment of pain, multiple sclerosis, epilepsy, post-traumatic stress disorder, and many other health conditions (Maccarone et al. 2007). Unfortunately, as a result of the emphasis on cannabis abuse and the current federal criminalization of cannabis, many mental health clinicians are uninformed about the potential benefits of medical cannabis in the treatment of health and mental health problems, and on their role in working with clients using medical cannabis. The purpose of this paper is to (1) provide a historical review of cannabis use and policy in the United States and the impact of current US policy on cannabis on clinicians' access to the latest research findings on medical cannabis and health outcomes, (2) to provide a brief synopsis of research on the endocannabinoid system, and (3) to provide information to clinicians who have patients that use medical cannabis as a part of their medical treatment regimen.

Historical Analysis of Cannabis Use in the United States

To understand cannabis use in the US one must have an understanding of the history of how the social construction of cannabis and its use has evolved over time. Social construction theory "proposes that most of what passes for knowledge in society is socially constructed, particularly common-sense knowledge that constitutes the reality of everyday life for the ordinary members of society" (Boeri and Lamonica 2017, p. 259). Furthermore, this theory posits that phenomena are created, modeled, and promoted within society (Boeri and Lamonica 2017).

✉ Jan Roberts
jlr725@nyu.edu

[1] NYU Silver School of Social Work, 429 E. 6th St., Apt D-1, New York, NY 10009, USA

Published online: 03 August 2018

The social construction of cannabis has transformed from viewing cannabis as a widely accepted and prescribed medication in the early 1900s to a highly demonized Schedule I drug in the 1970s; this shift occurred as a result of racism and propaganda reflecting the social and political perspectives of their times (Baum 2016). Consequently, the resulting US policy impacted the funding of research which then was used to further re-validate the existing US policy.

The Stigmatization of Cannabis

The use of cannabis was viewed as therapeutic, not recreational, until the early 1900s. During the 1920s, cannabis was used recreationally, mostly by wealthy individuals (Millhorn et al. 2009). However, the stigmatization increased in the 1930s as a growing number of Mexican users emigrated to the United States, and black jazz musicians became more popular with both groups using cannabis recreationally (Boeri and Lamonica 2017; Hudak 2016a). As a result of these changes, politicians began to lobby for the prohibition of cannabis (Hudak 2016a). The term cannabis, which had been used previously, was replaced by the term "marijuana" or "marihuana," a pejorative term used to link the substance to Mexican immigrants (Boeri and Lamonica 2017; Hudak 2016a). During the 1930s, propaganda films such as "Reefer Madness," were released depicting an unrealistic and frightening view of the consequences of cannabis use (Hudak 2016a). These films and accompanying propaganda, often racist in nature, were successful in scaring the public and driving usage underground. Consequently, politicians continued to institute other laws criminalizing cannabis, such as the Marihuana Tax Act of 1937.

Prohibition of Cannabis

Cannabis was never federally regulated or prohibited until the passage of the Marihuana Tax Act of 1937 (Boeri and Lamonica 2017). This law, which was vehemently opposed by the American Medical Association, did not specifically prohibit the use or sale of cannabis. However, it did place hefty levies on the substance which essentially crippled the economic production of cannabis (Boeri and Lamonica 2017; Ryan and Sharts-Hopko 2017; Szaflarski and Sirven 2017). The Marihuana Tax Act, coupled with anti-cannabis propaganda films and literature that effectively promoted cannabis as a dangerous drug with high potential for addiction, paved the groundwork for cannabis' prohibition at the federal level (Boeri and Lamonica 2017), which will be discussed later.

As the political and social unrest in the US heightened in the late 1960s and 1970s, the prohibition of cannabis was concretized. The intersection of the civil rights movement, social and political unrest, and the Vietnam war resulted in a hard-line approach in US policy called the "War on Drugs," the largest anti-drug campaign in US history (Kuzmarov 2009). Initiated by President Richard Nixon in 1971, the "War on Drugs" aimed to reduce drug use by criminalizing drug use (Sirin 2011). This "war" sought "to discredit liberal social ideology and eradicate public anxiety over Vietnam" (Kuzmarov 2009, p. 101). However, this policy campaign which focused on cannabis and heroin use arose from other motives as well. John Ehrlichman, a former aide to President Nixon, revealed in an interview in 1994 that protestors and African-Americans were the true target of the "War on Drugs" (Baum 2016). Ehrlichman was quoted as saying:

> The Nixon campaign in 1968, and the Nixon White House after that, had two enemies: the antiwar left and black people. You understand what I'm saying? We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities. We could arrest their leaders, raid their homes, break up their meetings, and vilify them night after night on the evening news. Did we know we were lying about the drugs? Of course we did (Baum 2016, p. 22)

This powerful statement reveals the biased impetus behind cannabis prohibition in US policy. With the advent of the United States Controlled Substance Act of 1970, cannabis' fate was sealed as a dangerous substance on par with heroin and LSD (Drug Enforcement Agency 2017). Viewing US drug policy through Goffman's notion of deviance and stigma's effect as a social control agent, the US drug policy has been effective in achieving Nixon's aim at targeting minorities through criminalization, mass incarceration, and further marginalization (Fornili 2018; Garner 2016; Goffman 1986; Szaflarski and Sirven 2017).

Cannabis as a Schedule I Drug

Nixon successfully continued his politically motivated efforts at linking cannabis with heroin and demonizing drug abuse. As part of Nixon's war on drugs initiative, and the passage of the Controlled Substances Act in 1970, the US Drug Enforcement Agency (DEA) created a system to categorize any substance or drug regulated by federal law based on their therapeutic use, safety, possibility for abuse, and potentiality for dependence. The DEA has created five categories of substances, referred to as "schedules," with "schedule I" including the most harmful substances and "schedule V" the least harmful (DEA 2017). Cannabis was declared as a Schedule I drug with DEA claiming that it has a high likelihood to be abused, that it has no recognized

medicinal efficacy, and that it cannot be used safely even under medical supervision (DEA 2017, p. 9).

As a result of this designation as a Schedule I drug, research on the efficacy and impact of cannabis has been severely restricted by the DEA (Bridgeman and Abazia 2017; National Academies 2017; Hudak 2016b; Pettinato 2017). In order to conduct research on Schedule I substances like cannabis, researchers must obtain separate permission from the DEA; the approval process for studying cannabis is more complicated for researchers than studying other Schedules II-V substances (Bridgeman and Abazia 2017). Another challenge to conducting research on cannabis is the actual procurement of quality cannabis for research (Bridgeman and Abazia 2017; Hudak 2016b). Issues such as poor quality, lack of strain variation among cannabis, and slow production of cannabis have negatively impacted researchers' abilities to conduct rigorous research in the US (Hudak 2016b). However, in countries such as Great Britain, Israel, Canada, and Spain, cannabis research has proliferated and has demonstrated positive health outcomes related to pain reduction, seizure reduction and a variety of other conditions (Americans for Safe Access 2017). These positive findings on the relationship of cannabis to improved physical and mental health outcomes are counter-indicative of the classification of cannabis as a Schedule I drug.

National Institute on Drug Abuse and the Gateway Hypothesis

Building upon the War on Drugs initiative in 1974, the National Institute of Drug Abuse (NIDA) was established "as the Federal focal point for research, treatment, prevention, training, services, and data collection on the nature and extent of drug abuse" (National Institutes of Health 2018). Research initiatives were supported through NIDA funding and directed by US policy. One of the most interesting NIDA supported works revolved around the "gateway hypothesis" (Setting the record straight on the phrase 'gateway drug' 2015).

The gateway hypothesis postulates that cannabis leads to abuse of harder and more dangerous drugs (Kleinig 2015). The gateway hypothesis, originally coined by Denise Kandel but promoted by Robert L. DuPont, the first Director of NIDA, was so powerful that it became a central hypothesis for cannabis research in mental health (Choo et al. 2008; Garner 2016; Kleinig 2015; Secades-Villa et al. 2015). Kandel's research was funded by NIDA with the specific intent to investigate cannabis as a potential "gateway" to harder substances (Setting the record straight on the phrase 'gateway drug' 2015). However, there have been recent questions to the validity of this hypothesis (Choo et al. 2008; Garner 2016; Kleinig 2015; Secades-Villa et al. 2015). Several studies have failed to find the direct causality between cannabis use and other harder illicit drug use and suggest other variables that might be of influence, such as behavioral issues or co-occurring mood disorders (Choo et al. 2008; Secades-Willa et al. 2015). The findings from these studies demonstrate that the use of the more dangerous substances, such as heroin and cocaine, are more likely related to emotional disorders than the use of cannabis (Choo et al. 2008). Consequently, the gateway hypothesis, which has served to reinforce current US drug policy, reflects an inherent bias and has been challenged as a simplistic and inaccurate (Kleinig 2015).

Therapeutic Uses of Cannabis

According to Pubmed, there are more than 40,000 empirical articles on cannabis and its molecular components (Pettinato 2017). Research on the effectiveness of cannabis has indicated that not only does cannabis provide relief from several specific diseases, but that cannabis may be able to prevent some health problems as well such as seizures, inflammation, irritable bowel syndrome, and pain (Pettinato 2017; Russo 2016a).

Understanding Cannabis and the Endocannabinoid System

Cannabis is a phytocannabinoid, a cannabinoid that naturally exists in the cannabis plant and that interacts with the endocannabinoid system (ECS), a naturally-occurring physiological system within the body that is responsible for maintaining cellular homeostasis and keeping the body in a state of wellbeing (Americans for Safe Access 2017; Pettinato 2017). The ECS is composed of neuromodulators, corresponding receptors, and signaling pathways which help regulate numerous physical functions (Maccarone et al. 2007; Gui et al. 2015; McPartland et al. 2014; Russo 2008, 2016a). Furthermore, the ECS "modulates virtually every brain region and thereby contributes to nearly every function of the CNS" (Hillard 2015, p. 3). A regulated endocannabinoid system results in healthy functioning within a body, whereas a dysregulated ECS results in pathological functioning through pain, mood disorders, inflammation, and neurogenerative diseases such as Alzheimer's, Parkinson's, and Huntington's disease (Hillard 2015; Maccarrone et al. 2007; Moeller and Woods 2015; Pettinato 2017; Russo 2016a, b; Sinclair 2016). In addition, healthy functioning of the ECS has been shown to reduce cancer, osteoporosis and rheumatoid arthritis (Gui et al. 2015; Moeller and Woods 2015; Pettinato 2017; Sinclair 2016).

The ECS is comprised of endocannabinoids, innate endogenous molecules such as Anandomide and 2-Arachidonoglycerol, that are critical to homeostasis, stress

management, and immune function (Lu and Mackie 2016; Russo 2016b). Endocannabinoids bind to receptors, such as receptors CB1 and CB2, which are found throughout the body and regulate homeostatic functioning (Sinclair 2016; Ward and Tuma 2014). Failure to produce enough endocannabinoids can result in dysregulation, i.e. improper functioning of the endocannabinoid system; this malfunctioning of the ECS is referred to as clinical endocannabinoid deficiency (McPartland et al. 2014; Russo 2008, 2016a). Cannabis is a phytocannabinoid that can supplement endocannabinoids in the ECS by attaching to receptors in order to assist in healthy functioning of the ECS (Lu and Potter 2017; Russo 2016b; Sinclair 2016). Cannabis' unique complex chemical makeup which is comprised of cannabinoids along terpenoids, essential oil-like compounds found in cannabis, synergize to boost the therapeutic potential of cannabis in affecting the ECS (Marcu 2016; McPartland et al. 2014; Russo 2008, 2016a, 2016b). Over one hundred cannabinoids have been found to be present in the cannabis plant (Marcu 2016). If a person's body does not produce enough endocannabinoids, then the chemical compounds in cannabis can serve to supplement the ECS to bring about its healthy regulation (Gui et al. 2015; McPartland et al. 2014; Sinclair 2016).

Current Research and Mental Health

There is a growing body of work related to cannabis use and behavioral health. Researchers have a better understanding of the ECS and mood regulation at a molecular level (Hill et al. 2009; Micale et al. 2013). Components of cannabis demonstrate antidepressant and anti-anxiety effects on animal models and the mechanisms are currently being identified (Walsh et al. 2017). For example, cannabidiol, a phytocannabinoid present in cannabis, has been found to produce antidepressant-like effects (Sartim et al. 2016). McLaughlin and Gobbi (2012) reported that low-doses of the phytocannabinoid THC, one of the major molecules found in cannabis, produces an anxiolytic response in animal models when directly injected into the medial pre-frontal cortex. In addition, studies on the ECS' and cannabis' impact on PTSD have produced some promising results (O'Neil et al. 2017). Cannabis has been successfully used to improve sleep and negative affect symptoms in people with PTSD (Walsh et al. 2017). A recent study of U.S. veterans found that cannabis "was associated with a retrospective self-reported 75% reduction in re-experiencing, avoidance, and arousal symptoms of PTSD" (Walsh et al. 2017, p. 22).

Research studies on the use of cannabis as a therapeutic tool in regulating moods are also showing promising results (Hill et al. 2009; Walsh et al. 2017). Another focus for researchers has been pain. Because of cannabis' known analgesic effect, researchers have worked to understand the impacts that ECS and cannabis have on pain relief (Woodhams et al. 2017); as a result, cannabis, as a known analgesic, has been suggested as a harm-reduction substitute for opiate use and opiate addiction (Lucas and Walsh 2017). In fact, in a study of over 1248 cannabis users, Corroon et al. (2017) reported that 36% of cannabis users reported that they use cannabis to avoid the use of opiates and to help manage their pain.

Issues to Consider for Therapeutic Use of Cannabis

Mental health clinicians need to have adequate education about cannabis and the issues that are important for healthy, therapeutic use. In order to best serve adult clients who utilize medical cannabis, mental health clinicians need to understand the issues related to healthy cannabis use. These include the entourage effect, the biphasic effect and dosage, the effect of different varieties of cannabis, method of consumption, and the role that cannabis can play in a harm reduction strategy for opioid addiction.

Determinants of the Effects of Cannabis

Historically, it was believed that the variety of cannabis, i.e., indica versus sativa, was the primary cause of the relatively different experiences of consumers. Research had demonstrated that many variables affect how cannabis is experienced. One's metabolism of cannabis, tolerance and method of consumption impact the effects of cannabis use. However, the individual molecular properties of cannabis- the ratios of chemical compounds found within the cannabis plant- are the main determinants of the effects of cannabis (Marcu 2016). Cannabis has over 100 different cannabinoids which produce separate unique effects (Marcu 2016). The most commonly known cannabinoids are THC and cannabidiol (Marcu 2016). THC is a cannabinoid that provides energy, stimulates hunger, and is chiefly responsible for the "high" feeling experienced when consumed. Cannabis varieties high in THC are often suggested for people with pain, nausea, depression or insomnia (Sinclair 2016). A second cannabinoid, cannabidiol (CBD), is known to produce anti-anxiety effects, reduce inflammation and pain without the high experienced with THC (Sinclair 2016). However, another compound widely known to influence the effects of cannabis are terpenes, a chemical compound that produce smells that often act like essential oils in producing excitatory or inhibitory responses (Sinclair 2016).

Entourage Effect

Since THC is known to produce psychoactive effects such as euphoria, feelings of being "high," increased laughter,

and increased awareness, there has been a push to reduce THC and look for only CBD-based products. However, research suggests that due to the "entourage effect," or the unique chemical makeup of the molecular compounds in the cannabis plant, these different cannabinoid molecules work collaboratively and more efficiently together than separated (Russo 2011). Cannabinoids and terpenoids both play important roles in the types of effects that cannabis provides to consumers (Russo 2011). Therefore, the grouped effects of the present cannabinoids and including terpenoids in the cannabis plant present greater potential for healing than an isolated, sole cannabinoid. This unique understanding of the entourage effect presents exciting research opportunities, but also makes replication of the unique chemical compound found in cannabis plants more challenging (Russo 2011).

Biphasic Effect and Dosage

Another issue to consider when discussing the role of cannabis in mental health treatment is the biphasic effect, which suggests that a drug can cause one reaction at a low dosage and an opposite reaction at a high dosage. Because of this effect, it is important to understand that overuse of cannabis can be damaging. Knowing the optimal dosage allows cannabis users to determine the appropriate amount needed to regulate their endocannabinoid system efficiently. It would bear to reason that since cannabis has potential for positive health outcomes, it can potentially be used for health purposes.

The use of cannabis use does not automatically translate to abuse. The excessive use of any substance, whether alcohol, benzodiazepines or pain medications such as opiates can lead to harmful consequences. A therapeutic dosage of cannabis should be enough to activate the ECS but not too much to dysregulate it. For example, cannabis using clients who experience a lack of motivation, increased anxiety, paranoia, or physiological problems like chronic vomiting syndrome, are demonstrating the effects of a dysregulated ECS (Richards 2017). Microdosing may modulate these effects and lead to healthier ECS functioning.

Method of Consumption

Method of consumption is another issue that needs to be considered when planning the therapeutic use of cannabis. Typical methods of consumption include "capsules, sublingual sprays, edible (oral) forms, infused oils (oral), tinctures, soft extracts, concentrated extracts, vaporizing, smoking (combustion) and topical oils, creams or ointments" (Sinclair 2016, p. 114). Each method of use has different effects on symptom relief. For example, for pain, edibles can provide more relief from symptoms for a longer period of time because of how they are metabolized in the liver (Sinclair 2016). Smoking or vaping, on the other hand, produces a more immediate, yet shorter duration of symptom relief (Sinclair 2016).

Impact on Opioid Epidemic

Currently, the U.S. is in the midst of a widespread opioid epidemic (Hsu 2016). Research has demonstrated that there is a negative correlation between legal access to cannabis and the reduction of deaths from opioids (Hsu 2016; Livingston et al. 2017). Research from Vyas et al. (2018) assert that states with medical cannabis laws to treat pain have fewer deaths than opioid related deaths than states without medical cannabis for pain laws.

It is widely known that cannabis use is a safer alternative to opiate use. Cannabis has been shown to have analgesic effects and does not impact the respiratory system as opioids do (Lucas and Walsh 2017; Pettinato 2017). Furthermore, research has demonstrated that patients who use cannabis along with opiates use significantly less opiates to control pain than patients who do not use cannabis (Boehnke et al. 2016). For patients with chronic pain for more than one year, cannabis has been shown to provide a better quality of life, improvements in physical functioning, improved cognitive function, and reduction of pain when compared to patients who use solely opiates (Ware et al. 2015). Although this is an emerging topic for researchers which needs to be explored more thoroughly, the risk of death associated with cannabis use are far less than the inherent physiological risk of death for opioid users due to the potential effect on the respiratory system (Lucas and Walsh 2017; Pettinato 2017).

Shifting Attitudes and the Need for Mental Health Researchers and Clinicians to Re-Evaluate their Approach

Despite federal law, currently 29 states have legalized medical cannabis (29 legal medical marijuana states and DC 2017). This populist-led change in laws at the state levels has result from anecdotal accounts and a substantial amount of literature demonstrating the positive benefits of cannabis for a variety of health conditions (Americans for Safe Access 2017). This is contributing to a shift in perspective and reduced stigmatization as the stories of therapeutic use as well as the increasing numbers and types of patients using cannabis continue to grow. The therapeutic use of cannabis calls for practitioners to be aware of the continued stigmatization and role of public policy that influences physicians as well as research funding.

Stigmatization of Cannabis Today

Cannabis use continues to be stigmatized, with federal policies in the US reinforcing this stigmatization. By continuing criminalization, society reinforces the notion of cannabis users as marginalized people. Even though medical cannabis in the US is legal in many states, the perceived stigmatization still occurs. Medical cannabis patients often express concerns "about being labeled a 'pothead' or 'stoner'" (Ryan and Sharts-Hopko 2017, p. 188). There are commonly held societal beliefs that medical cannabis users only want "to get high." One consequence of this continued stigmatization is that people are less likely to reveal their use of medicinal cannabis to their healthcare providers for fear of being further stigmatized (Ryan and Sharts-Hopko 2017).

Stigmatization even occurs related to the consumption method used for medical cannabis. Research indicates that medical cannabis patients view orally administered cannabis consumed through capsules, sublingually or via oral suspensions more favorably and with less stigma than traditional methods of consumption, such as smoking, using a water pipe, or vaping (Rudski 2014). In addition, research has indicated that the type of ailment being treated also plays into how others perceive medical cannabis (Lewis and Sznitman 2017). The less stigmatized an illness is, i.e. cancer versus HIV/AIDS, the less stigmatized is the use of medical cannabis for it (Lewis and Sznitman 2017).

Most clinical research on addiction focuses on the attitudes and measurements of stigma based on the substances used rather than the actual addictive behavior of the users (Lang and Rosenberg 2017). Unfortunately, focusing on the substances tend to negate the devastating effects that compulsive and addictive behaviors can have. Few studies have measured the experience and the positive impact of healthy cannabis use, while most studies focus on the dysfunction of the cannabis user (Garner 2016). The studies documenting the positive experience of cannabis use tend to be disregarded (Garner 2016).

Bias Among Researchers and Clinicians

Researchers have their own bias and stigmatization of cannabis which often is reflected in the research questions asked and the research that is conducted (Garner 2016). As indicated previously, since most of the research in the mental health field focuses primarily on cannabis use from a pathological lens, mental health educators lack resources that do not view cannabis from a pathological framework (Garner 2016). This skewed perspective on cannabis, coupled with the lack of education informing budding clinicians on current research on the endocannabinoid system and its effect on physical and behavioral function, leads to continued marginalization of cannabis users.

When discussing cannabis, many clinicians often express concerns about the effects of cannabis on the brain. However, current research on cannabis and brain functioning often provides confusing and contradictory information (Becker et al. 2018; Grant and Cahn 2005; Mokrysz et al. 2016; Pope et al. 2001). Many clinicians are also influenced by research focusing on the gateway hypothesis, as well as their internalized biases against cannabis and cannabis use. Research on mental health clinicians' attitudes toward cannabis is difficult to find. Identifying one's biases and counter-transference are vital for clinicians to provide quality clinical care to clients. A small study by Garner (2016) on seven graduate students who consumed cannabis revealed that even these students had internalized societal stigmatization and recognized that their own use was contrary to stereotypes of graduate students. In addition, the graduate students interviewed reported that the stereotypes and stigma around cannabis use led to feelings of internalized shame, increased secrecy, and fears of being judged by others. One participant was quoted as saying,

> Just as a graduate student in general I feel like it's something I have to hide. Um, I feel like it's not something you could admit and talk about with anyone because there is this persona that I have to represent (Garner 2016, p. 6)

In her findings, Garner (2016) reports that the students interviewed noted that their cannabis use provided positive benefits in their lives. Respondents reported that cannabis use provided self-awareness, a feeling of connection with others, and positive self-care (Garner 2016). These attributes starkly contrast with the internalized societal sense of shame also experienced by the respondents in this study.

In her conclusions, Garner (2016) suggests that clinicians need to be wary of their own bias and to recognize that cannabis may provide positive results for the respondents. Furthermore, Garner (2016) suggests that implications from this study should inform mental health clinical practice:

> Given the symbolic and facilitative role that marijuana played for many participants in respect to their identity, extracurricular enjoyment, and self-care, clinicians may also wish to explore the meaning of marijuana use as part of their case formulation before deciding whether such use is pathological or to what extent it will be a focus of treatment. (p. 12)

The findings suggest that mental health clinicians should identify their own biases and determine what type of role cannabis plays in their clients' lives before pathologizing the use (Garner 2016).

As stated earlier, the use of cannabis has been viewed through the lens of substance abuse, an approach that has reinforced the stigmatization of this substance and its

perception as a pathological, maladaptive coping strategy that is harmful to the individual and has no medical benefits. Current clinical training does not provide objective education about cannabis as a medicine, nor does it address the benefits that cannabis can provide. Mental health clinicians and other healthcare providers, including physicians, pharmacists, and nurses often lack up-to-date information based on scientifically rigorous research (Brooks et al. 2017; Evanoff et al. 2017; Moeller and Woods 2015; Pettinato 2017). Unfortunately, this lack of scientific knowledge reinforces the current US policy which pathologizes cannabis use. Consequently, clinicians are ineffective in their care, because they lack education around topics such as dosage, the effects of different varieties of cannabis, method of consumption and impact on mental health outcomes.

Currently, little research exists on the role of mental health practitioners working with adult clients using medical cannabis. As indicated previously, funded research has been relegated to the study of cannabis abuse and not on healthy or medical cannabis use. A recent EBSCO search of more than seven million sources on "healthy use of cannabis" and "healthy use of marijuana" yielded zero results pertaining to non-pathological use of cannabis. In addition, when performing another EBSCO search on "recreational use of cannabis" and "recreational use of marijuana," no studies linking cannabis use to healthy behavioral outcomes were reported. It is challenging to find researchers in mental health who are studying the healthy use of cannabis (University of British Columbia 2017a, b).

Conclusion

The federal cannabis prohibition policy and the DEA policy listing cannabis as a Schedule I drug has negatively impacted objective research. Past research has demonstrated a bias to view cannabis use pathologically often using the gateway hypothesis as its focus (Choo et al. 2008). Until recently, research has not focused on the efficacy of cannabis in treating certain health conditions despite cannabis being used for over 2000 years as a medicine.

Current international research and clinical experiences demand that mental health clinicians rethink their position around the use of cannabis. The Gateway Hypothesis is a simplistic view of cannabis use and ignores underlying behavioral and emotional issues that may influence negative coping behaviors. Cannabis has demonstrated positive benefits and the continued stigmatization adds to continued disconnection between clients and clinicians. Furthermore, the current environment hinders clinicians from providing evidence-based guidance and care that our clients deserve.

By observing their own biases around the stigmatization of cannabis use, mental health clinicians can provide better care for their clients. Reducing stigmatization among mental health clinicians is also necessary to provide clients with objective resources and helpful information about healthy cannabis use. Clinicians need to be educated on both the positive and negative effects of cannabis. In addition, they should be aware of varieties of cannabis, methods of consumption, and dosage. By having this knowledge, mental health clinicians can frame conversations with their clients in a more meaningful and therapeutic manner.

Currently, there is an emerging field of research about cannabis, the endocannabinoid system, and its impact on mental health. This area needs to be examined closely to objectively study the effects of cannabis use on health and wellbeing. There is a need to provide education for mental health clinicians by providing current evidence-based education around cannabis, including the endocannabinoid system, its effects on health outcomes, and role in mood regulation. Furthermore, there is an opportunity for educators and researchers in mental health to partner with basic science researchers in the understanding of some of the physiological effects of the endocannabinoid system and to bridge the gap between basic science and research in mental health clinical settings.

References

29 Legal Medical Marijuana States and DC. (2017). Retrieved from https://medicalmarijuana.procon.org/view.resource.php?resourceID=000881&print=true.

Americans for Safe Access. (2017). *Medical Cannabis in America- The Medical Cannabis Briefing Book* (*115th Congress*). Washington, DC: Americans for Safe Access.

Baum, D. (2016). Legalize it all: How to win the war on drugs. *Harper's Magazine*, 22–32.

Becker, M. P., Collins, P. F., Schultz, A., Urošević, S., Schmaling, B., & Luciana, M. (2018). Longitudinal changes in cognition in young adult cannabis users. *Journal of Clinical and Experimental Neuropsychology, 40*(6), 529–543. https://doi.org/10.1080/13803395.2017.1385729.

Boehnke, K. F., Litinas, E., & Clauw, D. J. (2016). Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *Journal of Pain, 17*(6), 739–744. Retrieved from http://www.sciencedirect.com/science/article/pii/S1526590016005678.

Boeri, M., & Lamonica, A. K. (2017). The social re-construction of marijuana as medicine. *Journal of Ethnographic & Qualitative Research, 11*(4), 257–276. Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=ssf&AN=124031510&site=eds-live.

Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal cannabis: History, pharmacology, and implications for the acute care setting. *Pharmacy and Therapeutics, 42*(3), 180–188.

Brooks, E., Gundersen, D. C., Flynn, E., Brooks-Russell, A., & Bull, S. (2017). The clinical implications of legalizing marijuana: Are physician and non-physician providers prepared? *Addictive Behaviors, 72*, 1–7. https://doi.org/10.1016/j.addbeh.2017.03.007.

Choo, T., Roh, S., & Robinson, M. (2008). Assessing the "gateway hypothesis" among middle and high school students in Tennessee. *Journal of Drug Issues, 38*(2), 467–492. Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edswss&AN=000257388800005&site=eds-live.

Ciccone, C. D. (2017). Medical marijuana: Just the beginning of a long, strange trip? *Physical Therapy, 97*(2), 239–248. https://doi.org/10.2522/ptj.20160367.

Corroon, J. M., Mischley, L. K., & Sexton, M. (2017). Cannabis as a substitute for prescription drugs - A cross-sectional study. *Journal of Pain Research, 10*, 989–998. https://doi.org/10.2147/JPR.S134330.

Drug Enforcement Agency. (2017). *Drugs of abuse: a DEA resource guide*. Washington, DC: United States Department of Justice.

Evanoff, A. B., Quan, T., Dufault, C., Awad, M., & Bierut, L. J. (2017). Physicians-in-training are not prepared to prescribe medical marijuana. *Drug and Alcohol Dependence, 180*, 151–155. https://doi.org/10.1016/j.drugalcdep.2017.08.010.

Fornili, K. S. (2018). Racialized mass incarceration and the war on drugs: A critical race theory appraisal. *Journal of Addictions Nursing (Lippincott Williams & Wilkins), 29*(1), 65–72.

Garner, E. (2016). A phenomenology of marijuana use among graduate students. *Indo-Pacific Journal of Phenomenology, 16*, 1–17. https://doi.org/10.1080/20797222.2016.1164997.

Goffman, E. (1986). *Stigma: Notes on the management of spoiled identity*. New York: Simon & Schuster.

Grant, I., & Cahn, B. R. (2005). Cannabis and endocannabinoid modulators: Therapeutic promises and challenges. *Clinical Neuroscience Research, 5*, 185–199.

Gui, H., Tong, Q., Qu, W., Mao, C., & Dai, S. (2015). The endocannabinoid system and its therapeutic implications in rheumatoid arthritis. *International Immunopharmacology, 26*, 86–91.

Hill, M. N., Hillard, C. J., Bambico, F. R., Patel, S., Gorzalka, B. B., & Gobbi, G. (2009). The therapeutic potential of the endocannabinoid system for the development of a novel class of antidepressants. *Trends in Pharmacological Sciences, 30*, 484–493. https://doi.org/10.1016/j.tips.2009.06.006.

Hillard, C. J. (2015). The endocannabinoid signaling system in the CNS: A primer. *International Review of Neurobiology*. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/26638763.

Hsu, J. (2016). Can medical cannabis break the painkiller epidemic? *Scientific American, 315*(3), 10–12. Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=118576938&site=ehost-live.

Hudak, J. (2016a). *Marijuana: A Short History*. Washington, D. C.: Brookings Institution Press. Retrieved from http://www.jstor.org/stable/10.7864/j.ctt1hfr1qj.

Hudak, J. (2016b). The DEA's marijuana decision is more important than rescheduling. Retrieved from https://www.brookings.edu/blog/fixgov/2016/08/11/the-deas-marijuana-decision-is-more-important-than-rescheduling/.

Kleinig, J. (2015). Ready for retirement: The gateway drug hypothesis. *Substance Use & Misuse, 50*(8), 971–975. https://doi.org/10.3109/10826084.2015.1007679.

Konkolÿ Thege, B., Colman, I., el-Guebaly, N., Hodgins, D. C., Patten, S. B., Schopflocher, D., & Wild, T. C. (2015). Social judgments of behavioral versus substance-related addictions: A population-based study. *Addictive Behaviors, 42*, 24–31. https://doi.org/10.1016/j.addbeh.2014.10.025.

Kuzmarov, J. (2009). The brass responds, part I: Nixon's war on drugs. *The myth of the addicted army* (pp. 101–120) University of Massachusetts Press.

Lang, B., & Rosenberg, H. (2017). Public perceptions of behavioral and substance addictions. *Psychology of Addictive Behaviors, 31*(1), 79–84. https://doi.org/10.1037/adb0000228.

Lewis, N., & Sznitman, S. R. (2017). You brought it on yourself: The joint effects of message type, stigma, and responsibility attribution on attitudes toward medical cannabis. *Journal of Communication, 67*(2), 181–202. https://doi.org/10.1111/jcom.12287.

Livingston, M. D., Barnett, T. E., Delcher, C., & Wagenaar, A. C. (2017). Recreational cannabis legalization and opioid-related deaths in colorado, 2000–2015. *American Journal of Public Health, 107*(11), 1827–1829. https://doi.org/10.2105/AJPH.2017.304059 Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=her&AN=125672932&site=eds-live.

Lu, D., & Potter, D. E. (2017). Cannabinoids and their receptors. In V. Preedy (Ed.), *Handbook of cannabis and related pathologies* (pp. 553–563). US: Academic Press.

Lu, H., & Mackie, K. (2016). An introduction to the endogenous cannabinoid system. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2015.07.028.

Lucas, P., & Walsh, Z. (2017). Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *International Journal of Drug Policy, 42*, 30–35. https://doi.org/10.1016/j.drugpo.2017.01.011.

Maccarrone, M., Battista, N., & Centonze, D. (2007). The endocannabinoid pathway in Huntington's disease: A comparison with other neurodegenerative diseases. *Progress in Neurobiology, 81*(5), 349–379. https://doi.org/10.1016/j.pneurobio.2006.11.006.

Marcu, J. (2016). An overview of major and minor phytocannabinoids. In V. Preedy (Ed.), *Neuropathology of drug addictions and substance misuse: Foundations of understanding, tobacco, alcohol, cannabinoids and opioids* (pp. 672–678).

McLaughlin, R. J., & Gobbi, G. (2012). Endocannabinoids, emotional behavior and psychiatric illness: Cannabinoids and emotionality: A neuroanatomical perspective. *Neuroscience, 204*, 134–144. https://doi.org/10.1016/j.neuroscience.2011.07.052 Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=edselp&AN=S0306452211008773&site=eds-live.

McPartland, J. M., Guy, G. W., & Di Marzo, V. (2014). Care and feeding of the endocannabinoid system: A systematic review of potential clinical interventions that upregulate the endocannabinoid system. *PLOS ONE*. https://doi.org/10.1371/journal.pone.0089566.

Micale, V., Di Marzo, V., Sulcova, A., Wotjak, C. T., & Drago, F. (2013). Endocannabinoid system and mood disorders: Priming a target for new therapies. *Pharmacology & Therapeutics, 138*(1), 18–37. https://doi.org/10.1016/j.pharmthera.2012.12.002.

Millhorn, M., Monaghan, M., Montero, D., Reyes, M., Roman, T., Tollasken, R., & Walls, B. (2009). North Americans' attitudes toward illegal drugs. *Journal of Human Behavior in the Social Environment, 19*(2), 125–141. https://doi.org/10.1080/10911350802687075.

Moeller, K. E., & Woods, B. (2015). Pharmacy students' knowledge and attitudes regarding medical marijuana. *American Journal of Pharmaceutical Education, 79*(6), 1–8.

Mokrysz, C., Curran, H. V., Landy, R., Gage, S. H., Munafo, M. R., & Roiser, J. P. (2016). Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study. *Journal of Psychopharmacology, 30*(2), 159–168. Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com.proxy.library.nyu.edu/login.aspx?direct=true&db=edswsc&AN=000368806700006&site=eds-live.

National Academies. (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press. https://doi.org/10.17226/24625.

National Institutes of Health. (2018). The NIH almanac. Retrieved from https://www.nih.gov/ about-nih/what-we-do/nih-almanac/national-institute-drug-abuse-nida.

O'Neil, M. E., Nugent, S. M., Morasco, B. J., Freeman, M., Low, A., Kondo, K., & Kansagara, D. (2017). Benefits and harms of plant-based cannabis for posttraumatic stress disorder: A systematic review. *Annals of Internal Medicine, 167*(5), 332. https://doi.org/10.7326/M17-0477.

Pettinato, M. (2017). Medicinal cannabis: A primer for nurses. *Nursing, 47*(8), 40–46. https://doi.org/10.1097/01.NURSE.0000521022.07638.35.

Philipsen, N., Butler, R. D., Simon-Waterman, C., & Artis, J. (2014). Continuing education: Medical marijuana: A primer on ethics, evidence, and politics. *The Journal for Nurse Practitioners, 10*, 633–640. https://doi.org/10.1016/j.nurpra.2014.05.015.

Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun-Todd, D. (2001) Neuropsychological performance in long-term cannabis users. *Archives in General Psychiatry*, 58, 909–915.

Richards, J. R. (2017). Cannabinoid hyperemesis syndrome: A disorder of the HPA axis and sympathetic nervous system? *Medical Hypotheses, 103*, 90–95. https://doi.org/10.1016/j.mehy.2017.04.018 Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com.proxy.library.nyu.edu/login.aspx?direct=true&db=edselp&AN=S0306987717301342&site=eds-live.

Rudski, J. M. (2014). Treatment acceptability, stigma, and legal concerns of medical marijuana are affected by method of administration. *Journal of Drug Issues, 44*(3), 308–320. https://doi.org/10.1177/0022042613511441.

Russo, E. B. (2008). Clinical endocannabinoid deficiency (CECD) - can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? (reprinted from *Neuroendocrinology*, vol 25, pg 31–39, 2004) Retrieved from http://proxy.library.nyu.edu/login?url=http:// search.ebscohost.com/login.aspx?direct=true&db=edswsc&AN=000255490000002&site=eds-live.

Russo, E. B. (2011). Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *British Journal of Pharmacology, 163*(7), 1344–1364. https://doi.org/10.1111/j.1476-5381.2011.01238.x Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=67057512&site=eds-live.

Russo, E. B. (2016a). Clinical endocannabinoid deficiency reconsidered: Current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment- resistant syndromes. *Cannabis and Cannabinoid Research, 1*(1), 154–165. https://doi.org/10.1089/can.2016.0009.

Russo, E. B. (2016b). Beyond cannabis: Plants and the endocannabinoid system. *Trends in Pharmacological Sciences, 37*, 594–605. https://doi.org/10.1016/j.tips.2016.04.005.

Ryan, J., & Sharts-Hopko, N. (2017). The experiences of medical marijuana patients: A scoping review of the qualitative literature. *The Journal of Neuroscience Nursing: Journal of the American Association of Neuroscience Nurses, 49*(3), 185–190. https://doi.org/10.1097/JNN.0000000000000283.

Sartim, A. G., Guimarães, F. S., & Joca, S. R. L. (2016). Antidepressant-like effect of cannabidiol injection into the ventral medial prefrontal cortex—Possible involvement of 5-HT1A and CB1 receptors. *Behavioural Brain Research, 303*, 218–227. https://doi.org/10.1016/j.bbr.2016.01.033.

Secades-Villa, R., Garcia-Rodríguez, O., Jin, C. J., Wang, S., & Blanco, C. (2015). Probability and predictors of the cannabis gateway effect: A national study. *International Journal of Drug Policy*. https://doi.org/10.1016/j.drugpo.2014.07.011.

Setting the record straight on the phrase '*gateway drug*' (audio file). (2015). National Public Radio, Inc. (NPR)

Sinclair, J. (2016). An introduction to cannabis and the endocannabinoid system. *Australian Journal of Herbal Medicine, 28*(4), 107–125. Retrieved from http://search.informit.com.au/documentSummary;dn=484958787162768;res=IELHEA.

Sirin, C. V. (2011). From Nixon's war on drugs to Obama's drug policies today: Presidential progress in addressing racial injustices and disparities. *Race, Gender & Class, 18*(3–4), 82–99.

Stiles, B. L., & Kaplan, H. B. (1996). Stigma, deviance, and negative social sanctions. *Social Science Quarterly* (*University of Texas Press*), *77*(3), 685–696. Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=buh&AN=24258918&site=eds-live.

Szaflarski, M., & Sirven, J. I. (2017). Social factors in marijuana use for medical and recreational purposes. *Epilepsy & Behavior, 70*(Part B), 280–287. https://doi.org/10.1016/j.yebeh.2016.11.011.

University of British Columbia. (2017a). *Zach Walsh*. Retrieved from http://psyo.ok.ubc.ca/ faculty/walsh.html.

University of British Columbia. (2017b). *Zach Walsh Research Lab Therapeutic, Recreational, & Problematic Substance Use*. Retrieved from http://blogs.ubc.ca/walshlab/research- interests/.

Vyas, M. B., LeBaron, V. T., & Gilson, A. M. (2018). The use of cannabis in response to the opioid crisis: A review of the literature. *Nursing Outlook, 66*(1), 56–65. Retrieved from http://proxy.library.nyu.edu/login?url=http://search.ebscohost.com.proxy.library.nyu.edu/login.aspx?direct=true&db=edsbl&AN=vdc.100055277355.0x000001&site=eds-live.

Walsh, Z., Gonzalez, R., Crosby, K., Thiessen, M.,S., Carroll, C., & Bonn-Miller, M. (2017). Medical cannabis and mental health: A guided systematic review. *Clinical Psychology Review, 51*, 15–29. https://doi.org/10.1016/j.cpr.2016.10.002.

Ward, S. J., & Tuma, R. F. (2014). Endocannabinoids. In R. Daroff & M. Aminoff (Eds.), *Encyclopedia of the neurological sciences, vol 2* (pp. 42–47). London: Elsevier Inc. https://doi.org/10.1016/B978-0-12-385157-4.00041-5.

Ware, M. A., Wang, T., Shapiro, S., & Collet, J. (2015). Cannabis for the management of pain: Assessment of safety study (COMPASS). *Journal of Pain, 16*(12), 1233–1242. Retrieved from http://www.sciencedirect.com/science/article/pii/S1526590015008378.

Woodhams, S. G., Chapman, V., Finn, D. P., Hohmann, A. G., & Neugebauer, V. (2017). The cannabinoid system and pain. Neuropharmacology, *124*, 105–120. https://doi.org/10.1016/j.neuropharm.2017.06.015.

Jan Roberts is a Licensed Clinical Social Worker and CEO of Partners in Health and Wellbeing, a multisite mental health and integrative care practice in the Mid-Atlantic region. Ms. Roberts is currently completing her doctorate at New York University's Silver School of Social Work.

SCHEDULING CANNABIS: A PREPARATORY DOCUMENT FOR FDA'S 8-FACTOR ANALYSIS ON CANNABIS

A SCIENTIFIC APPROACH FOR CONGRESS, DRUG ENFORCEMENT ADMINISTRATION, AND DEPARTMENT OF JUSTICE

Prepared by Americans for Safe Access (2016)

Reviewed by Jahan Marcu, Ph.D., Ethan Russo MD, Lumir Hanus, Ph.D., Roger Pertwee, Ph.D., Steph Sherer, and Jason Schechter, Ph.D.

The research and analysis in this report was conducted by
Americans for Safe Access Foundation, a 501(c)(3) non-profit organization.

Publication date July 2016

With over 100,000 active members in all 50 states, Americans for Safe Access (ASA) is the largest national member-based organization of patients, medical professionals, scientists and concerned citizens promoting safe and legal access to cannabis for therapeutic use and research. ASA works to overcome political and legal barriers by creating policies that improve access to medical cannabis for patients and researchers through legislation, education, litigation, grassroots actions, advocacy and services for patients and their caregivers, the medical cannabis industry, and governments.

Learn more about ASA at AmericansForSafeAccess.org.

1624 U Street NW, Suite 200, Washington, D.C. 20009
Phone: 1-888-929-4367 fax: 202.857.4273

TABLE OF CONTENTS

I. INTRODUCTION

Over the past decade, national polls in the United States (U.S.) have consistently ranked support for medical *Cannabis* among Americans at around 80%. A recent national poll showed that support for medical *Cannabis* now stands at 89% [1]. Over 300 million Americans live in states with some kind of law allowing for the use of medical *Cannabis* and over 2 million patients are legally accessing medical *Cannabis* under their physician's supervision.

Federal laws and regulations surrounding the medical use of *Cannabis* have been based on politics rather than science dating back to the passage of the Marijuana Tax Act of 1937. Today, *Cannabis* remains a Schedule I drug under the Controlled Substance Act (CSA), which means it has no accepted medical use. Various efforts to reschedule *Cannabis* in the U.S. based on medical and scientific information have consistently been stymied by the Drug Enforcement Administration (DEA).

In April of this year, the DEA reported to Congress that they will be issuing a response to yet another rescheduling petition by mid-year 2016. This comes more than four years after receiving a petition from elected officials. This is an opportunity for the DEA to move *Cannabis* to a less-restrictive schedule (or removed from the CSA entirely) in order to boost research on the drug and the development of *Cannabis* products that doctors could openly recommend or eventually prescribe. However, the DEA continually moves away from a sensible research and public health approach to *Cannabis*[2]. Past reports on *Cannabis* research provided by the DEA have not included enough of the modern scientific articles published in the last 20 years and cites poorly designed studies that other researchers have failed to reproduce. Additionally, the DEA largely uses its own media and other non-scientific information to support its policy decisions on research and medical uses.

The DEA has little to risk by recommending that *Cannabis* be placed in another schedule status. Rescheduling would not legalize *Cannabis*, would not make *Cannabis* possession or cultivation by non-qualified or non-licensed individuals any less illegal under federal law, and it would be unlikely to end the standoff between the federal government and the states that have legalized *Cannabis*.

Medical *Cannabis* patients are not the only voices calling on the DEA to reschedule *Cannabis*. Governors, the U.S. Supreme Court, the American Medical Association, the American College of Physicians, and the American Public Health Association are just a few of the other institutions calling for the DEA to act[3]. However, given the DEA's history on *Cannabis* and the fact that the DEA is the only federal agency that has not moved forward on the subject of *Cannabis*, we are not anticipating a wholly scientific response.

Americans for Safe Access (ASA) has pulled together world experts to create our own 8-factor analysis. In the following report, hundreds of modern peer-reviewed research studies are included for the analysis of the potential risks and benefits of *Cannabis* based on scientific evidence that researchers have largely been able to reproduce over the last decade. The independent 8-factor analysis provided here is a thorough peer-review document on the scientific data of *Cannabis*, containing all the information that is requested to consider rescheduling a drug. Our hope is that this document is used as a foundation for the public, Congress, and the Department of Justice to use to counter any DEA findings.

II. BACKGROUND

The U.S.'s history with *Cannabis* as a medicine dates back to the 1800's. *Cannabis* was a part of the American Pharmacopoeia until 1942. The political interference in the regulation of *Cannabis* as a medicine and subsequently the control of medical *Cannabis* research originates with the passage of the Marijuana Tax Act in 1937. Over the objections of the American Medical Association, the U.S. enacted the first federal law designed to restrict access to *Cannabis*, even for medical purposes[4].

Cannabis is now regulated by the CSA. At the time the CSA was being drafted in 1970, Assistant Secretary of Health, Roger O. Egeberg recommended that *Cannabis* temporarily be placed in Schedule I, pending the findings of the National Commission on Marihuana and Drug Abuse. President Richard Nixon appointed Pennsylvania Governor Raymond Shafer to chair the Commission. On March 22, 1972, the Commission presented its report, "Marijuana, A Signal of Misunderstanding," to Congress which concluded that the risks of using *Cannabis* were minimal and that general use did not jeopardize health, lead to experimentation with other drugs, or cause criminal activity, and specifically recommended the decriminalization of marijuana for personal use.

The recommendations provided in the Commission's report conflicted with many of the provisions provided in the Comprehensive Drug Abuse Prevention and Control Act and the CSA. President Nixon needed to reject the recommendations and formally declare a "war on drugs." Despite the Commission's recommendations to permit the medical and personal use of *Cannabis*, President Nixon enacted the Comprehensive Drug Abuse Prevention and Control Act.

Title II of the act, formally known as the CSA, places drugs into one of five categories, or schedules. *Cannabis* was restricted to Schedule I, reserved for substances with no medical value and a high potential for abuse; all use of the substance became strictly prohibited. Examples of other Schedule I drugs include heroin and LSD. Paradoxically, synthetic forms of THC, the most powerful psychoactive chemical component of *Cannabis*, are classified as Schedule III. Schedule III is reserved for drugs that exhibit medical value and have a mild potential for abuse. Other Schedule III drugs include ketamine, buprenorphine, hydrocodone, and codeine.

Cannabis may be reclassified in one of two ways; by an act of Congress or via administrative channels. The DEA could remove *Cannabis* from the list of Schedule I drugs through the rulemaking process in the same way they have handled dronabinol and other substances. However, the CSA also provides for a rulemaking process by which the general public may petition the U.S. Attorney General to reclassify *Cannabis* in accordance with the relevant scientific data.

Rescheduling and research petitions have previously been met with marginal success due to government agencies using antiquated and inefficient review processes. The first petition to reschedule was submitted in 1972 and was denied after 22 years of court appeals. In the summer of 1986, the DEA administrator initiated public hearings on *Cannabis* rescheduling. The hearings lasted two years, involving testimony from more than 60 researchers, doctors and their patients, and thousands of pages of documentation. On September 6, 1988, DEA Chief Administrative Law Judge Francis L. Young ruled that *Cannabis* did not meet the legal criteria of a Schedule I prohibited drug and should be reclassified. He declared that *Cannabis* in its natural form is "one of the safest therapeutically active substances known to man... It

would be unreasonable, arbitrary, and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance...The provisions of the (Controlled Substances) Act permit and require the transfer of marijuana from Schedule I to Schedule II."

However, DEA Administrator John Lawn overruled Young's determination. Lawn said he decided against rescheduling *Cannabis* based on testimony and comments from numerous medical doctors who had conducted detailed research and were widely considered experts in their respective field, undisclosed meetings, and data. In 1994, the D.C. Court of Appeals finally affirmed the DEA Administrator's power to overrule a DEA Judge's decision, with little scientific evidence required to support the Administrators position (Alliance for Cannabis Therapeutics v. DEA. 15 F.3d 1131). In summary, without disclosing the experts or the data they may have provided to overturn the Judge's decision, the petition to reschedule was officially denied by the DEA after an Administrator overturned the DEA court ruling.

The second attempt began in 1995 and was denied in April 2001. Another petition was received in 2002 (76 FR 40552), but was denied by the DEA in July 2011. In 2002, the Coalition for Rescheduling *Cannabis*, made up of several individuals and organizations, including ASA, filed a petition to reclassify *Cannabis* for medical use. That petition was denied by the DEA in July 2011, after ASA sued the Obama Administration for unreasonably delaying the answer. The appeal to the D.C. Circuit was the first time in nearly 20 years that a federal court reviewed the issue of whether adequate scientific evidence exists to reclassify *Cannabis*. Before the January ruling, the D.C. Circuit had never granted plaintiffs the right to sue when seeking reclassification of *Cannabis*.

After many years of frustration, patients and advocates began turning to their states for protection, rights, and access, eventually passing the first medical *Cannabis* law in 1996. Today 42 states, D.C., Puerto Rico, and Guam have passed some kind of law allowing the use of *Cannabis*. However, all of these state laws operate in conflict with the federal law and until 2014, following the passage of the Rohrabacher-Farr amendment to the Commerce, Justice, Science and Related Agencies Act (CJS), experienced federal enforcement including threats, raids, arrest, and prosecution by U.S. attorneys.

Patient advocates claim that *Cannabis* is treated unlike any other controlled substance and that politics have inappropriately dominated over medical science on this issue. Advocates point to a research approval process for *Cannabis*, controlled by the National Institute on Drug Abuse (NIDA), which is unique, overly rigorous, and effectively hinders meaningful pre-clinical and therapeutic research. In its appeal brief, ASA argued that the DEA has no "license to apply different criteria to marijuana than to other drugs, ignore critical scientific data, misrepresent social science research, or rely upon unsubstantiated assumptions, as the DEA has done in this case[5]."

ASA cited more than 200 peer-reviewed studies in its appeal, but the D.C. Circuit held that plaintiffs must produce evidence from Phase II and Phase III clinical trials -- usually reserved for companies trying to bring a new drug to market -- in order to show *Cannabis'* medical efficacy. Long term, Phase II and III studies on medical *Cannabis* will simply not be approved by the DEA or the NIDA under the current standards regulating their national monopoly on *Cannabis* produced for clinical research, unless *Cannabis* were to be rescheduled under the Conventions. Subsequently, ASA filed an appeal in January 2012, with the D.C. Circuit, which was heard on October 16th, 2012 and later denied[5].

In November of 2011, following the DEA's denial of the 3rd rescheduling petition in 30 years, Governors Christine Gregoire (D-WA) and Lincoln Chafee (I-RI) jointly filed a petition to reclassify marijuana for medical use[6]. At a press conference announcing the filing, Governor Gregoire said, "It is time to show compassion and common sense, the people getting hurt in all of this are patients." In the rescheduling petition, the governors cited as many as 700 peer-reviewed research studies and reports on medical marijuana, and asked for public hearings, "so that the government can hear from doctors and scientists[5]."

In April 2016, the DEA responded to a letter from U.S. Senators in 2015[i] asking when a response would be given to the nearly five-year-old rescheduling petition. The DEA has said that they expect to issue their response to this petition my "mid-year 2016[5] ."

It should be noted that while the DEA has failed to reschedule the whole plant form of *Cannabis*, the primary psychoactive drug on the plant, associated with nearly all of its negative side effects, was rescheduled to Schedule II in 1985 and Schedule III in 1999. This is a pure form of THC known as dronabinol.

Today more than 2 million patients have access to medical *Cannabis* and *Cannabis* products under state laws and over 300 million Americans live in states where this is an option. Many of these states have adopted standards for regulating *Cannabis* products in these markets as botanical standards with appropriate monographs. A recent United States Pharmacopoeia (USP) meeting cited the American Herbal Pharmacopoeia (AHP) *Cannabis* monograph as the current standard for regulating *Cannabis* as a medicine in the U.S. The USP cannot release an official monograph for *Cannabis* until it is rescheduled to a much less restrictive category[7].

Patient advocacy groups such as ASA, continue to put pressure on the U.S. Presidential administration, but are also lobbying Members of Congress to reclassify *Cannabis* for medical use. The Compassionate Access, Research Expansion, and Respect for States (CARERS) Act has also been introduced, which in addition to rescheduling *Cannabis* would allow states to establish *Cannabis* access laws and product safety regulations without interference by the federal government, and would remove current obstacles to research.

III. EVALUATING *CANNABIS* UNDER THE 8 FACTORS

FACTOR 1: CANNABIS' ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

The CSA defines Cannabis or marijuana as the following:

All parts of the plant Cannabis Sativa L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term does not include the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination. 21 U.S.C. 802(16).

The term "abuse" is not defined in the CSA. However, the legislative history of the CSA suggests the following in determining whether a particular drug or substance has a potential for abuse*:*

A. Individuals are taking the substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

B. There is a significant diversion of the drug or substance from legitimate drug channels.

C. Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such substances.

D. The substance is so related in its action to a substance already listed as having a potential for abuse to make it likely that it will have the same potential for abuse as such substance, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.

> *Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970) reprinted in U.S.C.C.A.N. 4566, 4603.*

In response to criteria for abuse as listed in a-d above, this section examines scientific publications related to toxicology, toxic and lethal dosing, abuse potential, adverse events, public health outcomes, and the role of *Cannabis* in psychiatric disorders (Anxiety, Depression, and Related Mood Disorders).

A. INDIVIDUALS ARE NOT TAKING THE SUBSTANCE IN AMOUNTS SUFFICIENT TO CREATE A HAZARD TO THEIR HEALTH OR TO THE SAFETY OF OTHER INDIVIDUALS OR TO THE COMMUNITY.

To determine the potential health hazards of a substance the human clinical toxicological data should be reviewed. The field of toxicology and related areas of study exist to define and codify the toxic effects exerted by administered drugs on the body and mind. The toxicology associated with *Cannabis* administration in humans has been extensively measured, via numerous pre-clinical and clinical studies. Using batteries of standardized tests, each study sought to compare brain health, function, and/or cognition of an individual affected with *Cannabis* to that of a "normally" functioning individual[8-11].

There has been a historical and intensive effort to address those public health concerns related to the use of *Cannabis* and its effects on cognition[5]. Negative effects on cognition or brain health (i.e., "toxic" effects) are most often defined as any statistically significant deviation from a "normal" mean[12-16]. This mean is calculated by quantifying a battery of neuropsychological tests (i.e., memory, emotional cueing, and coordination tests) and brain imaging techniques (e.g. computed tomography [CT] or magnetic resonance imaging [MRI]). Whereas the former is useful for assessing aberrant behavioral, motoric, and learning effects, imaging is most useful in determining any abnormalities in physical brain structure and/or function caused by the intake of a drug.

Since concerns of *Cannabis* toxicity were first raised over perceived negative effects of *Cannabis* on brain health, unbiased investigation has remained somewhat problematic due to restrictions and objectives of traditional funding sources as they relate to *Cannabis* research[17-20]. When negative ideological rhetoric guides health policy, rather than empirical scientific findings, reports of outcomes are often exaggerated or distorted prior to public presentation[17,20-23]. Further, the results of extensive animal research may not appropriately represent the complex realities found in human populations, and thus proper human studies must be adequately controlled and conducted to define actual toxicology[24].

Hence, the articles cited in this report are derived from evidence generated by controlled human studies, with a preference towards investigations of standardized preparations of *Cannabis* of known purity, provenance, content, and pharmacokinetic profile, over studies that are not properly controlled for variables or that do not include any dose-response, neuroimaging, neurochemical, or anatomical correlates.

An overview of existing research on the subject of potential harm to human brain health from the effects of *Cannabis* is provided below.

Evidence Regarding Toxic and Lethal Dosing of Cannabis Preparations

A lethal toxic overdose of *Cannabis* or its preparations has never been documented, nor has there ever been evidence that an attainable lethal dose of plant cannabinoids exists for humans. In basic research, human primary brain cells, cultured *in vitro,* exposed to excessively high amounts of THC – the primary active compound found in *Cannabis* – do not suffer any measurable toxic effects such as apoptosis or necrosis[25].

Drugs used in medicine are routinely given what is called an LD_{50}[26]. The LD_{50} rating indicates at what dosage 50% of test subjects receiving a drug will die as a result of drug-induced toxicity. Whereas toxicological investigations are meant to evidence the LD_{50} of a drug, currently there is no known LD_{50} either for *Cannabis* or for any of its major components in humans. While a number of studies have *attempted* to determine an appropriate LD_{50} rating for *Cannabis* in test animals, researchers have continuously been unable to give animals enough natural *Cannabis* to induce a death.

According to the U.S. Drug Enforcement Administration (DEA) hearing testimonials, the accepted theoretical calculations for an LD_{50} of *Cannabis* were originally derived from a 1969 article by Todd Mikuriya, MD, which originated from a two-page 1968 position paper (without attributed authors) in the *Journal of the American Medical Association*[27,28]. In his paper, Mikuriya also estimated the lethal doses for *Cannabis* based on references to two previous papers by Loewe[29,30]. Neither prior to, nor since, has there been any real-life evidence of a human *Cannabis* toxicity-induced death to validate Mikuriya's estimated LD_{50}.

At present, it is estimated that the *human* toxicity of *Cannabis* is around 1:20,000 or 1:40,000. In layman terms, this means that in order to induce death, a *Cannabis* smoker would have to consume 20,000 to 40,000 times as much *Cannabis* as is contained in one *Cannabis* cigarette[31-33].

A U.S. NIDA-supplied *Cannabis* cigarette weighs approximately 0.9 g. Therefore, a person would have to consume nearly 1,500 *pounds* of *Cannabis* within a 15-minute period to induce a theoretically lethal response. Unlike opiates, *Cannabis* compounds, such as THC, do not depress respiration and cannot depress respiratory drive due to sparse receptor density in medullary respiratory centers of the human brain[34,35]. In practical toxicological terms, *Cannabis* alone simply cannot induce a lethal outcome as a result of drug-related toxicity.

Based on current understanding of basic toxicity research – sedation, cytotoxicity, genotoxicity, etc. – *Cannabis* and its components seem to have a uniquely wide safety margin[36-39]. To date, there has never been a single well-documented case of human fatality attributable to an overdose of *Cannabis* or its components, and no experimental or non-extrapolated LD_{50} can be attributed to a toxic or lethal overdose of *Cannabis* or a preparation thereof.

Clinical Toxicological Studies of Cannabis and Brain Function: IQ and Psychological Tests

Numerous assessments of brain function and IQ have been carried out in cohorts or groups studied from nearly every part of the world. The available evidence on effects of *Cannabis* on the brain come from wide-ranging human studies in the Caribbean, Latin America, North America, the Mediterranean, South Asia (Australia, New Zealand) and Europe. Most studies find a significant difference in brain function related to current *Cannabis* use (i.e., the day of the test), but show no consistent, reproducible, or significant long-term effects when study participants remain abstinent[40]. Results of long-term *Cannabis* use on brain health are often confusing and not statistically significant. As one clinical researcher noted in a review, "current human observations on the effects of marijuana [*Cannabis*] on development are sparse and contradictory[41]".

A review and summary of the existing human clinical evidence is provided below:

Clinicians in Jamaica administered a series of 19 neuropsychological tests to both chronic *Cannabis* users and naïve controls with no major differences between groups, except that the *Cannabis* users scored significantly higher on the Wechsler Adult Intelligence Scale (WAIS) Digit Span performance ($p<0.05$)[42]. The authors concluded that "there is no evidence that long-term use of *Cannabis* is related to chronic impairment[42]".

A study of [*Cannabis*] hashish users and naïve controls, matched for age and socio-economic status, noted no differences in total on Performance IQ (PIQ) scores on the WAIS, but the controls performed somewhat better on three subtests involving Comprehension, Similarities, and Digit Symbol Substitution[43]. However, with less than a 7 PIQ difference, normally found in Greece population studies, the authors were led to conclude that "these observations do not provide evidence of deterioration of mental abilities in hashish users[42]."

An extensive battery of neuropsychological tests showed no *Cannabis*-induced pathological changes in a Costa Rican population study. The authors stated, "we failed to uncover significant differences between user and nonuser groups – even in those subjects who had consumed *Cannabis* for over 18 years[44]". When a follow-up study was performed on some of the members of this long-using cohort, initially there were significant differences claimed, but a subsequent critical analysis of the results reported that the effects were reduced below a meaningful statistical significance[45,46].

Another study investigated the effects of *Cannabis* on "cognitive decline" in 1,318 adults under the age of 65, over a period of 12 years. Using the Mini-Mental State Examination (MMSE), the study evidenced no significant differences in the degree of decline amongst heavy, light, and *non*-users of *Cannabis*[8,47].

The book *Cannabis and Cognitive Functioning* is a series of summarized studies in which the author studied subjects using *Cannabis* at least twice a week, on average, for a period of 3 years[48]. The author stated (p. 227), "the weight of the evidence suggests that the long-term use of *Cannabis* does not result in any severe or grossly debilitating impairment of cognitive function." The author did note more subtle difficulties in attention parameters, including an increased predilection for subtle distraction, loose

associations, and likelihood of intrusion errors during memory tasks. In another review of cognitive effects of *Cannabis* by the same author, it was observed that "the long term risks for most users are not severe and their effects are relatively subtle…[49]"

A North American study on individuals aged 30-55 years old divided participants into 3 groups: 1) current daily users who had smoked *Cannabis* at least 5,000 times, 2) former users who had smoked *Cannabis* at least 5,000 times but had used *Cannabis* no more than 12 times in the prior 3 months, and 3) non-users, who had not consumed *Cannabis* more than 50 times in their lives[40]. Subjects underwent a 28-day washout period with tests performed at 0, 1, 7, and 28 days of abstinence. This study found that "users showed virtually no significant differences from control subjects on a battery of 10 neuropsychological tests[40]." The authors also concluded that former heavy users who had not consumed *Cannabis* in the last 3 months "showed no significant differences from control subjects on any tests during testing days." This study suggests that any induced cognitive deficits attributable to *Cannabis* use exist as reversible phenomena, associated with recent *Cannabis* exposure and not due to any irreversible toxicity.

A New Zealand birth cohort study, involving 1,037 participants, found an average drop in IQ of 8 points (within a somewhat higher degree of variability; +/- 14 IQ points) at age 38 in *Cannabis* users that had used at least 4 days per week, versus non-users[50]. The authors stated, "a limitation is that we obtained information on past-year *Cannabis* dependence and self-reported frequency of *Cannabis* use with no external validation of use (e.g., biological assays)[50]."

Another New Zealand study of 111 participants found that "current users of *Cannabis* containing CBD (a second and non-psychoactive cannabinoid found in natural *Cannabis*), as well as former users, showed no structural or neurochemical hippocampal differences compared with controls[12]." The experimental cohort that was exposed to THC and no reported CBD demonstrated temporary changes in hippocampal volumes, but these effects were not significant if the users reported using *Cannabis* containing CBD. The authors stated "users exposed to CBD and former users did not differ from controls on any measure[12]."

Most recent findings suggest that low to moderate adolescent *Cannabis* use is associated neither with IQ nor with lower educational performance once adjustment is made for potential confounding data – in particular, adolescent cigarette use[11]. A sample of 2,235 teenagers participated in a United Kingdom (UK) study, which adjusted for pre-exposure to *Cannabis*, cigarette use, alcohol use, childhood mental-health symptoms, and behavioral problems. *Cannabis* use itself was not found to be causally related to lower IQ or poorer educational performance. The authors concluded that "modest *Cannabis* use in teenagers may have less cognitive impact than epidemiological surveys of older cohorts have previously suggested[11]."

In regards to long-term cognitive effects of *Cannabis* use, a 2012 literature review of 11 peer-reviewed studies evaluating *Cannabis*' potential impact on cognitive function of over 1,000 subjects concluded, "The results of our meta-analytic study failed to reveal a substantial, systematic effect of long-term, regular *Cannabis* consumption on the neurocognitive functioning of users who were not acutely intoxicated[51]".

No scientifically significant negative neuropsychological sequelae have yet been attributable to *Cannabis*

usage. Arguably, some of these studies remain limited by a number of factors that need to be controlled in future investigations. Primarily, *Cannabis* use and dosing needs to be confirmed in users with biological and chemical tests, as issues of dosing and patterns of use are confounding factors when not adjusted for. "The results of our meta-analytic study fail[s]…to reveal a substantial, systematic effect of long-term, regular *Cannabis* consumption on the neurocognitive functioning of users who were not acutely intoxicated[51]".

Review of Toxicology of Cannabis Use in Brain Imaging Studies

Several studies have looked at small patient cohorts and have failed to find evidence of either permanent or consistent types of brain damage, abnormalities, structural brain changes, or brain tissue volume of either white or grey matter[48,52-56]. Human studies on brain structural and functional changes employing CT scans or MRIs are summarized below.

A 1977 study employed CT scans on 19 men with long durations of heavy *Cannabis* usage. Results showed no significant changes in either the ventricles or sub-arachnoid spaces[53]. The authors criticized a prior study for lacking controls on antecedent head trauma or other causes of neurological damage[54]. In the same issue of the *Journal of the American Medical Association*, an additional study on another cohort of 12 heavy *Cannabis* smokers displayed no CT abnormalities[55].

In 1983, brain CT scans were studied from 12 subjects who smoked more than 1 g of *Cannabis* daily for 10 years. Out of the 12 subjects, only 1 subject with a concomitant history of alcoholism showed any abnormalities compared to controls[56,57].

In 2000, no abnormalities were ascertained in a study that employed automated imaging analysis with MRI to examine 18 young/heavy *Cannabis* users. The authors stated "frequent marijuana use does not produce clinically apparent MRI abnormalities or detectable global or regional changes in brain tissue volumes of gray or white matter, or both combined[58]." One of the leading experts in the field of *Cannabis*' cognitive effects and dependence, Dr. Nadia Solowij, stated in a 2001 publication that "there is no evidence from human studies of any structural brain damage following prolonged exposure to cannabinoids[48]."

A 2015 study based in Colorado – a U.S. state that allows *Cannabis* use for qualifying adults – examined brain morphology (via volume measurements) in a sample of 29 *adult* daily *Cannabis* users versus 29 non-users, and a sample of 50 *adolescent* daily users versus 50 non-users[59]. The researchers measured the following areas and structures of the human brain, each understood to be associated with *Cannabis* use, as follows: the grey matter, nucleus accumbens, amygdala, hippocampus, and cerebellum. The results showed no statistically significant differences between daily users and non-users, in either volume or shape, in any region of interest. The authors concluded, "the results indicate that, when carefully controlling for alcohol use, gender, age, and other variables, there is no association between marijuana use and standard volumetric or shape measurements of subcortical structures[59]."

Claims of brain damage and cerebral atrophy are not supported by current evidence. When controlling for pertinent variables such as age, gender, and history of alcohol use, research has not been able to show any association between the use of *Cannabis* and changes in subcortical structures[59].

Abuse Potential, Dependence Potential and Adverse Reactions in Humans

Cannabis dependence or *Cannabis* use disorders are an increasingly recognized problem, principally driven by Δ^9-THC[60,61]. Although standardized *Cannabis* preparations such as nabiximols, dronabinol, and flower tops (Bedrocan; Dutch Cannabis) have a very low street value and diversion is rare, all THC containing medicines share a dependence liability. However, fundamental differences exist between patients receiving licensed or regulated medicine and commercial/recreational smokers of *Cannabis* obtained in the black market[60,61]. Of clear significance are variations in active cannabinoid and other constituents, and purity. There is also a fundamental difference in the *motivations* of users; recipients of a medicine typically seek to relieve their symptoms *without* experiencing cognitive disturbance[62].

Currently available standardized preparations of *Cannabis* have been found to have a very low abuse potential. Two examples of this are dronabinol an oral preparation of THC isolated from the *Cannabis* plant, and nabiximols, a recently licensed *Cannabis* medicine, approved and available in 27 countries, that contains equal amounts of THC and the synergistic non-intoxicating CBD. Dronabinol has also been proposed, and has demonstrated efficacy in limited trials, as a treatment for *Cannabis* use disorders[63].

Cannabis strains that are inhaled can contain varying ratios of active constituents, and thus may vary in a range of effects and may therefore have a higher abuse potential than dronabinol or nabiximols[64]. CBD also demonstrates a low abuse potential and has been shown to not significantly enhance the effects of THC or positive subjective effects of *Cannabis*[65].

The incidence of intoxication and euphoria during clinical trials of nabiximols has been very low, reported by only 2.2% percent of patients[9]. Significant tolerance was not recorded during long-term dosing, and abrupt withdrawal from long-term use produced only mild and transient disturbance of sleep, mood, or appetite in a minority of subjects with no concomitant withdrawal syndrome[60].

No cases of abuse or diversions of these medicines have been reported. This reassuring profile with regard to abuse potential is consistent with clinical experience of nabilone and dronabinol, which have been available by prescription for decades[66]. In published research articles, abuse or diversion is reported as “rare and isolated” and no evidence of street market for these drugs has been detected.

In an abuse liability study of experienced *Cannabis* smokers, higher doses of nabiximols *did* show evidence of abuse potential in comparison with placebo, but scored consistently lower on a dose-for-dose basis than dronabinol. The apparent difference in risk profile is likely a consequence of the presence of CBD in whole *Cannabis* preparations. In brain imaging and cognitive studies, participants reporting use of *Cannabis* containing a significant content of CBD have been demonstrated not to differ from control subjects with respect to either brain volume or reported results on a battery of neuropsychological tests.

The evidence to date suggests that abuse or dependence of standardized, regulated, or licensed *Cannabis* preparations is likely to occur only in a very small proportion of recipients.

Compared to nabiximols, inhaled *Cannabis* preparations have a higher abuse potential. Nabiximols also exhibits less non-serious psychological side effects as compared to oral THC preparations such as dronabinol[31,67]. Although the presence of THC in *Cannabis*-based preparations could lead to abuse or dependence, this possibility has not yet emerged with significance in clinical trials of standardized preparations of *Cannabis* administered via either the oral or oral-mucosal route. This area of investigation would benefit from further exploration in greater detail of inhaled *Cannabis* preparations.

Serious and Non-Serious Adverse Events and the Use of Medical Cannabis Preparations

Under international guidelines, a "serious adverse event" is defined as any untoward medical occurrence that requires admission to a hospital or prolongation of an existing admission, causes congenital malformation, results in persistent or significant disability or incapacity, is life threatening or results in death. A "nonserious adverse event" is defined as any untoward medical occurrence in a patient or participant; the event need not have a causal relation to the treatment. The guidelines of the International Conference on Harmonization define the 'expectedness' of an adverse event, whereby an "unexpected" adverse event is one for which "the nature or severity ... is not consistent with the applicable product information[68,69]."

A recent investigation on a cohort of 215 individuals with chronic non-cancer pain examined the safety issues of a standardized herbal *Cannabis* product (12.5% THC). The standardized *Cannabis* was dispensed to eligible subjects for a one-year period. The control group consisted of participants with chronic pain, who were not dispensed *Cannabis*. The primary outcomes measured consisted of serious adverse events and non-serious adverse events. Secondary safety outcomes included pulmonary and neurocognitive function and standard hematology, biochemistry, renal, liver, and endocrine function. Other parameters included pain and other symptoms, mood, and quality of life. The median daily *Cannabis* dose was 2.5 g/d. There was no difference in risk of serious adverse events between groups. Medical *Cannabis* users were at an increased risk of non-serious adverse events, but these were mild to moderate. There were no differences in secondary safety assessments. The authors conclude, "This study suggests that the adverse effects of medical *Cannabis* are modest and comparable quantitatively and qualitatively to prescription cannabinoids. The results suggest that *Cannabis* at average doses of 2.5g/d in current *Cannabis* users may be safe…[39]."

The next set of identified adverse events discussed and used in the subsequent text were part of an investigation that coded the adverse events to the highest standard of reporting, according to the Medical Dictionary for Regulatory Activities headings "system organ classes" and "preferred terms[70,71]."

Verification of data extraction methods and use of coding according to the Medical Dictionary for Regulatory Activities were verified by a medically qualified reviewer.

Numerous reports have attributed adverse effects to *Cannabis* as an associated risk factor for psychosis and neurocognitive effects[39]. Many of these reports either focus on recreational use *without* requiring a standardized *Cannabis* product, or do not employ biological assays to confirm and assess recent *Cannabis* use in participants[38,57,72,73]. The research summary and review below consists mainly of controlled, blinded studies on adverse events concerning medical *Cannabis* preparations.

A meta-analysis of 31 studies (23 randomized controlled trials and 8 observational studies) included an analysis of *Cannabis* side effects (such as dizziness and acute anxiety)[9]. *Cannabis* medicines included in the analysis comprised of an oral-mucosal *Cannabis* spray preparation (nabiximols), oral THC (dronabinol), and oral THC-CBD. The median duration of *Cannabis*-based medicine exposure was 2 weeks (ranging from 8 hours to 12 months). The meta-analysis identified a total of 4,779 adverse events reported amongst participants assigned to the intervention.

Most of the adverse events, 4,615 (96.6%), were not serious[9]. Amongst these studies, the most commonly reported non-serious side effect was dizziness (15.5%). However, the study did find 164 *serious* adverse events. The most frequent categories of serious adverse events among medical *Cannabis* product users were respiratory (16.5%), gastrointestinal (16.5%), and nervous system disorders (15.2%), whereas nervous system disorders were the most frequently reported among the control group (30.0%). Relapse of multiple sclerosis (21 events [12.8%]), vomiting (16 events [9.8%]), and urinary tract infection (15 events [9.1%]) were the most commonly reported serious adverse events among people assigned to receive medical *Cannabis* preparations. There was no evidence of a higher incidence of serious adverse events following medical *Cannabis* use compared with controls among a meta-analysis of adverse events and medical *Cannabis* preparations[9].

In January of 2016, a clinical trial with a synthetic modulator (BIA 10-2474) of the endocannabinoid system was abruptly interupted[74]. This synthetic drug inhibited the activity of fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of the endocannabinoid anandamide (AEA, arachidonoyl ethanolamide), thus increasing the concentrations of AEA available to stimulate the endocannabinoid system[75]. All of the pharmaceutical companies with active programs testing FAAH inhibitors voluntarily suspended their trials after the disaster of BIA 10-2474 from the Portuguese pharmaceutical company Bial, whose phase I study in healthy subjects in France left one person brain dead and five others hospitalized[76].

FAAH is also responsible for the degradation of many other fatty acid amides in the brain and body. Inhibiting FAAH not only increases the concentration of anandamide, but also the concentrations of other fatty acid amides[77]. As the mechanism of action is entirely different from that of THC, which binds to cannabinoid receptors[78], synthetic modulators of the endocannabinoid system should be seen as entirely different to cannabinoids or *Cannabis* in terms of their potential side effects and should be judged separately.

Short-term use of existing standardized medical *Cannabis* and *Cannabis* products appear to increase the

risk of non-serious adverse events. Risks associated with long-term *Cannabis* use are poorly characterized in published clinical trials and observational studies; however, the cognitive effects observed in long-term users do not appear to be permanent in nature[40]. With the exception of very limited studies on synthetic endocannabinoid system modulators, *Cannabis* medicines do not appear to cause significant serious adverse events. Three tables summarizing documented effects on controlled studies with a standardized preparation of *Cannabis* are provided below.

Table 2 Adverse Events Observed in Multiple Sclerosis (MS) Patients Using Cannabis Extract (Cannador®, Synthetic THC (Marinol), or Placebo

Adverse event	Short-term study (15 weeks; *n* = 611)			Long-term study (52 weeks; *n* = 502)		
	THC (Marinol; 10–25 mg)	*Cannabis extract (Cannador)* †	Placebo	THC (Marinol; 10–25 mg)	*Cannabis extract (Cannador)* †	Placebo
Dizzy or lightheadedness	59%	50%	18%	8%	10%	2%
Sleep	35%	40%	33%	8%	8%	9%
Spasms or stiffness	34%	33%	33%	14%	15%	14%
Gastrointestinal tract	30%	37%	20%	9%	12%	7%
Miscellaneous	28%	30%	22%	7%	7%	7%
Pain	26%	24%	32%	10%	17%	10%
Dry mouth	26%	20%	7%	2%	1%	1%
Weakness or reduced mobility	25%	23%	20%	10%	12%	16%
Bladder	24%	26%	23%	10%	12%	15%
Infection	15%	16%	17%	9%	11%	11%
Tremor or lack of coordination	12%	10%	8%	5%	2%	2%
Depression or anxiety	10%	9%	8%	6%	6%	5%
Numbness or paraesthesia	9%	7%	7%	5%	4%	4%
Vision	6%	8%	2%	2%	2%	0%
MS-relapse or exacerbation*	-	-	-	5%	6%	6%
Falls*	-	-	-	4%	7%	3%
Memory or concentration*	-	-	-	2%	2%	1%
Other skin problems*	-	-	-	1%	5%	6%
Pressure sores*	-	-	-	0%	1%	3%

† Cannabis extract contained 2.5 mg of Δ^9-THC equivalent, 1.25 mg of CBD, and 5% other cannabinoids per capsule.

* Not measured in the short-term study.

Source: Zajicek et al. (2003, 2005).

Table 1 Side Effects of the Cannabis Extract Sativex®

Adverse event	Acute studies		Long-term studies
	Cannabis (n = 644)	Placebo (n = 587)	*Cannabis*
Ear and labyrinth disorders			
Vertigo	4.3%	1.4%	2.3%
Eye disorders			
Blurred vision	2.2%	0.3%	1.1%
Gastrointestinal disorders			
Constipation	2.2%	0.7%	4.2%
Diarrhea	3.0%	1.5%	11.5%
Dry mouth*	7.9%	2.4%	8.3%
Nausea	10.6%	5.3%	12.8%
Oral discomfort*	2.6%	2.7%	2.9%
Oral pain*	3.3%	3.9%	7.7%
Vomiting	2.6%	1.5%	6.0%
General disorders and administration site conditions			
Application site pain*	3.3%	3.4%	5.0%
Fatigue	13.0%	7.8%	10.1%
Feeling abnormal	2.6%	0.5%	3.2%
Feeling drunk	4.5%	0.3%	4.4%
Asthenia	5.1%	2.2%	3.9%
Metabolism and nutrition disorders			
Increased appetite	2.0%	0.5%	0.9%
Nervous system disorders			
Balance disorder	2.5%	0.7%	4.2%
Disturbance in attention	4.5%	0.0%	4.4%
Dizziness	32.0%	10.2%	27.6%
Dysgeusia	4.7%	1.7%	8.0%
Lethargy	2.2%	0.9%	3.3%
Somnolence	8.9%	2.7%	8.2%
Psychatric disorders			
Disorientation	4.8%	0.9%	3.5%
Euphoric mood	2.6%	1.0%	3.8%

Source: Physician product information for the use of Sativex in the UK (GW Pharmaceuticals)

[1] Possible application site reaction.

Table 3 Side Effects Observed in a State Clinical Trial on Oral THC and Smoked Cannabis Conducted in California in the 1980s

Adverse event	Smoked cannabis (unknown dose n=98)	Oral THC (unknown dose n=257)
Dry mouth	56.5%	44.8%
Sedation	52.1%	64.0%
Dizziness	33.1%	26.8%
Ataxia	27.1%	12.8%
Elated mood	26.6%	24.4%
Confusion	26.6%	31.6%
Anxiety	20.2%	18.8%
Depressed	18.1%	13.2%
Perceptual	15.9%	22.8%
Fantasizing	10.7%	11.6%
Orthostatic	7.5%	12.8%
Panic/Fear	7.5%	7.6%
Tachycardia	6.4%	10.0%

Source: Musty and Rossi (2001).

Toxicology, Adverse Events, and Abuse

While few significant negative health sequelae are attributable to long-term *Cannabis* usage, ongoing human use of cannabinoids as medicine will continue to elucidate the emergence of negative effects. Clinically relevant risks and public health concerns associated with long-term cannabinoid use have yet to be satisfactorily demonstrated, perhaps due to the comparatively mild withdrawal effects of THC, its primary active compound. Based on current understanding of basic toxicity research, *Cannabis* and its components seem to have a uniquely wide safety margin. Notably cannabinoids do not depress respiratory drive, unlike opiates[34]. To date, there has never been a single documented case of human fatality attributable to an overdose of *Cannabis* or its cannabinoids. Results of meta-analytic studies have thus far failed to reveal any substantial, systematic effect of long-term, regular *Cannabis* consumption that is not reversed by abstinence.

Pulmonary issues associated with *Cannabis* smoking include chronic bronchitis, particularly chronic cough, and sputum production, with more variable effects on wheezing and generally negative effects on breathlessness. However, these issues are avoidable by using vaporizer/volatilizer technology or alternative routes of administration[79,80]. Importantly, lifetime use of *Cannabis* smoking is not associated with an increase incidence of lung cancer[81].

Another confounding factor affecting a clearer understanding of long-term, chronic *Cannabis* use is the prevalence of serious adverse events concerning untoward *Cannabis contaminants*. Lung infection from bacterial and fungal contamination of plant materials, lead and other heavy metals poisoning, bronchial irritation from foreign particulate matter such as tiny pieces of broken glass, concomitant use of tobacco, calamus and other cholinergic compounds[82,83]– some side effects, both serious and non-serious, are due to contaminated products found on the black market.

Access to *Cannabis* products manufactured under appropriate quality assurance/quality control conditions – such as those properly standardized *Cannabis* products now available in 27 countries – are associated with significantly lower prevalence of negative health issues, both serious and non-serious. The illegality of *Cannabis* is a threat to the safety of using *Cannabis* as a medicine. Programs for supporting qualified individuals to access *Cannabis*, global product safety guidelines, or licensed/regulated *Cannabis* testing facilities help to ensure that the rights of medical consumers are respected.

How Safe is Cannabis?

Research continues to demonstrate that *Cannabis* and its preparations have an excellent safety profile. According to the Drug Awareness Warning Network Annual Report, published by the Substance Abuse and Mental Health Services Administration (SAMHSA), which contains a statistical compilation of all drug deaths that occur in the U.S., not a single death has ever been recorded due to the use of *Cannabis*.

DEA Chief Administrative Law Judge, Francis Young, in response to a petition to reschedule *Cannabis* under federal law concluded in 1988 that, "*In strict medical terms marijuana is far safer than many foods we commonly consume.... Marijuana in its natural form is one of the safest therapeutically active substances*

known to man. By any measure of rational analysis marijuana can be safely used within the supervised routine of medical care[32]."

Public Health Outcomes

The effects of drug or substance abuse related to public health outcomes should be considered and evaluated in comparison to other drugs and substances[24,84-86]. Previous analysis has shown that *Cannabis* smokers are 2.6 times more likely to have a psychotic-like experience than compared to non-smokers[87,88]. By comparison, people who smoke tobacco are 20 times more likely to get lung cancer than those who do not smoke. To put this in perspective, over 5,000 men, 20-25 years old would need to stop using the drug in order to ostensibly prevent one episode of schizophrenia. Along with this is the paradox that while cases of schizophrenia have decreased in the last 30 years, *Cannabis* use has increased substantially amongst like populations[87,88].

Proper assessment of the harms caused by the misuse of drugs can inform policy makers when making decisions towards health, policing, and social care. The research study and figures discussed below apply a multi-criteria decision analysis (MCDA) model to demonstrate a range of drug harms. This research, based in the UK, provides the most recent comprehensive research published on comparing the harms of various drugs[89,90].

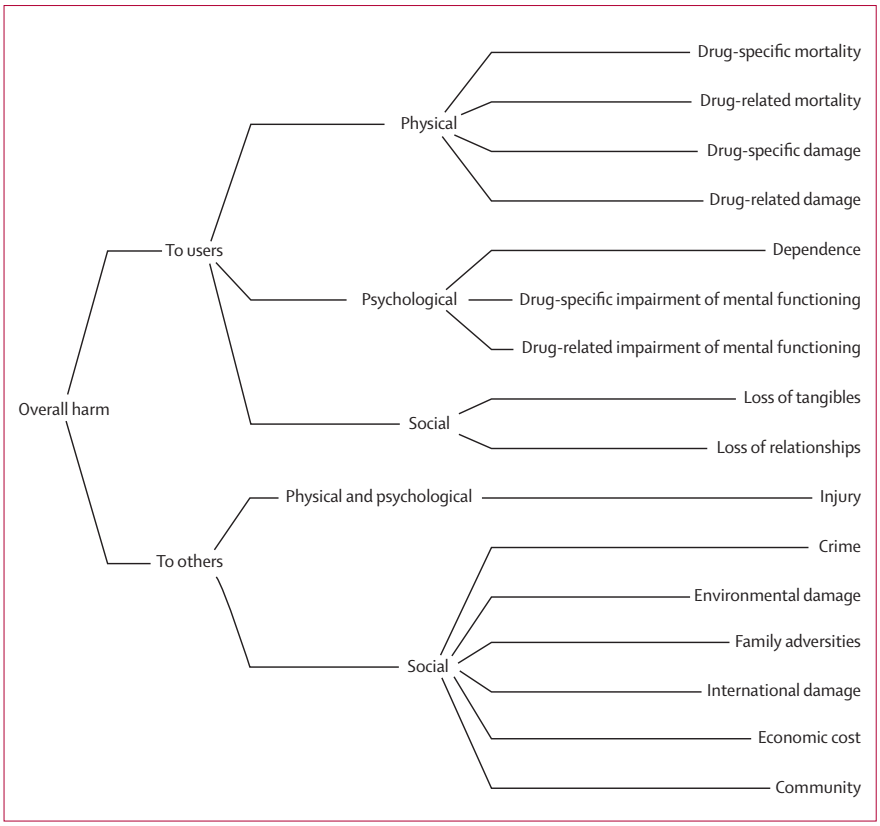


Figure 1) Evaluation criteria organized by harms to users and harms to others, and clustered under physical, psychological, and social effects. The above figure demonstrates how drug harm is measured; essentially the two major factors are harm to the drug user and harm to others.

From: Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: A multicriteria decision analysis. *The Lancet*, *376*(9752), 1558–1565. http://doi.org/10.1016/S0140-6736(10)61462-6

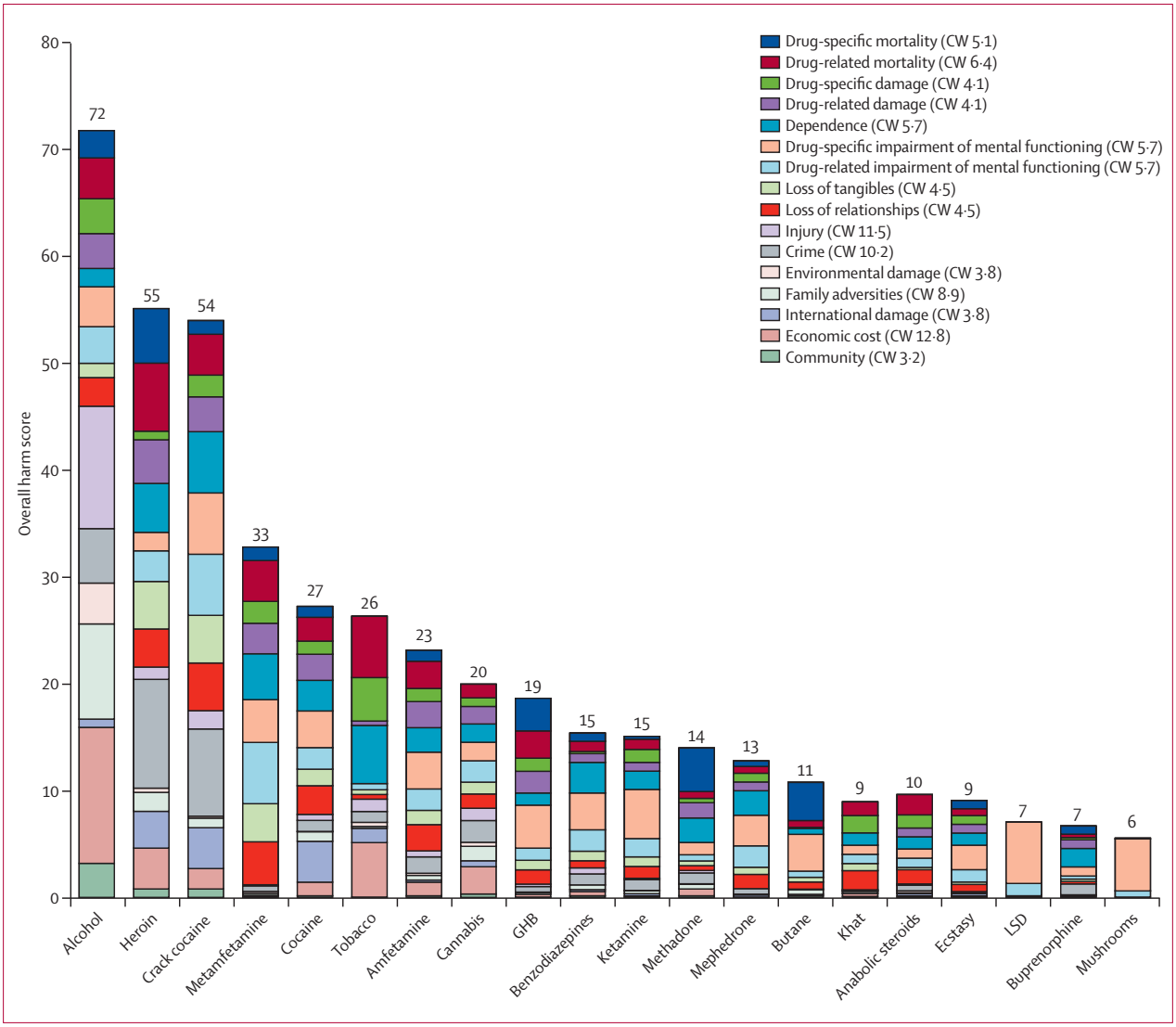


Figure 2*:* Overall weighted scores for each of the drugs

The colored bars indicate the part scores for each of the criteria. The key shows the normalized weight for each criterion. A higher weight indicates a larger difference between the most harmful drug on the criterion and no harm. CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide. The scores were generated according to the International Classification of Diseases, tenth revision of the Diagnostic and Statistical Manual of Mental Disorders, fourth revision. Nutt et al. (2010). Drug harms in the UK: a multicriteria decision analysis. *The Lancet*, *376*(9752), 1558–1565.

Definitions: **Drug-specific mortality** Intrinsic lethality of the drug expressed as ratio of lethal dose and standard dose (for adults). **Drug-related mortality** The extent to which life is shortened by the use of the drug (excludes drug-specific mortality)—eg, road traffic accidents, lung cancers, HIV, suicide **Drug-specific damage** Drug-specific damage to physical health—eg, cirrhosis, seizures, strokes, cardiomyopathy, stomach ulcers **Drug-related damage** Drug-related damage to physical health, including consequences of, for example, sexual unwanted activities and self-harm, blood-borne viruses, emphysema, and damage from cutting agents. **Dependence** The extent to which a drug creates a propensity or urge to continue to use despite adverse consequences (ICD 10 or DSM IV) **Drug-specific impairment of mental functioning** Drug-specific impairment of mental functioning—eg, amfetamine-induced psychosis, ketamine intoxication **Drug-related impairment of mental functioning** Drug-related impairment of mental functioning—eg, mood disorders secondary to drug-user's lifestyle or drug use **Loss of tangibles** Extent of loss of tangible things (eg, income, housing, job, educational achievements, criminal record, imprisonment) **Loss of relationships** Extent of loss of relationship with family and friends **Injury** Extent to which the use of a drug increases the chance of injuries to others both directly and indirectly—eg, violence (including domestic violence), traffic accident, fetal harm, drug waste, secondary transmission of blood-borne viruse. **Crime** Extent to which the use of a drug involves or leads to an increase in volume of acquisitive crime (beyond the use-of- drug act) directly or indirectly (at the population level, not the individual level). **Environmental damage** Extent to which the use and production of a drug causes environmental damage locally—eg, toxic waste from amfetamine factories, discarded needles. **Family adversities** Extent to which the use of a drug causes family adversities— eg, family breakdown, economic wellbeing, emotional wellbeing, future prospects of children, child neglect. **International damage** Extent to which the use of a drug in the UK contributes to damage internationally—eg, deforestation, destabilisation of countries, international crime, new markets. **Economic cost** Extent to which the use of a drug causes direct costs to the country (eg, health care, police, prisons, social services, customs, insurance, crime) and indirect costs (eg, loss of productivity, absenteeism). **Community** Extent to which the use of a drug creates decline in social cohesion and decline in the reputation of the community.

Members of the UK's Independent Scientific Committee on Drugs, and two invited specialists, met for a 1-day interactive workshop to score 20 drugs on harms assessment. This panel of drug-harm experts were convened to establish scores for 20 representative drugs that were relevant to the UK and which span the range of potential harms and extent of use. The harms were assessed according to a set of 16 criteria developed by the Advisory Council on the Misuse of Drugs (the UK Government committee on drug misuse). Of the 16 criteria, nine related to the harms that a drug produces in the individual and seven were in relation to the harms of another. Drugs were scored out of 100 points, and criteria were weighted to indicate their relative importance. Overall, alcohol showed to be the most harmful drug (overall harm score 72), with heroin (55) and crack cocaine (54) in second and third places.

Provided by Nutt et al. (2010), and created from data obtained from the workshop, Figure 2 shows a comparison amongst drugs of abuse across different scheduling and control status, with each colored bar representing a different criterion. For example, Drug-Specific Mortality, representing reported average occurrences of deaths from the substances over time, is on the top of each column. Alcohol, heroin, butane, and GHB display a notable association with higher risk of death from consumption, while *Cannabis*, anabolic steroids, khat, and LSD show very low or no association with mortality. A limiting factor of this and other data discussed here is that the substances are only scored for harm and weighted without scores or criteria regarding medical use. Another important limiting factor is that Nutt et al.'s calculations of *Cannabis* harm are somewhat overstated due to their consideration of *legal* harms in their process. Ideally, only medical factors would be the sole determinants of risk.

This is not the first study of its kind and previous research found similar results. The findings of Nutt et al. (2010) lend support to previous work in the UK, the Netherlands, the U.S. and elsewhere, confirming that the present drug classification systems have little relation to empirical evidence of harm[57,87-93]. These studies also subscribe to the conclusions of previous expert reports, that aggressively targeting alcohol harms is a valid and necessary public health strategy.

	Physical harm				Dependence				Social harm			
	Mean	Acute	Chronic	Intravenous	Mean	Pleasure	Psychological dependence	Physical dependence	Mean	Intoxication	Social harm	Health-care costs
Heroin	2·78	2·8	2·5	3·0	3·00	3·0	3·0	3·0	2·54	1·6	3·0	3·0
Cocaine	2·33	2·0	2·0	3·0	2·39	3·0	2·8	1·3	2·17	1·8	2·5	2·3
Barbiturates	2·23	2·3	1·9	2·5	2·01	2·0	2·2	1·8	2·00	2·4	1·9	1·7
Street methadone	1·86	2·5	1·7	1·4	2·08	1·8	2·3	2·3	1·87	1·6	1·9	2·0
Alcohol	1·40	1·9	2·4	NA	1·93	2·3	1·9	1·6	2·21	2·2	2·4	2·1
Ketamine	2·00	2·1	1·7	2·1	1·54	1·9	1·7	1·0	1·69	2·0	1·5	1·5
Benzodiazepines	1·63	1·5	1·7	1·8	1·83	1·7	2·1	1·8	1·65	2·0	1·5	1·5
Amphetamine	1·81	1·3	1·8	2·4	1·67	2·0	1·9	1·1	1·50	1·4	1·5	1·6
Tobacco	1·24	0·9	2·9	0	2·21	2·3	2·6	1·8	1·42	0·8	1·1	2·4
Buprenorphine	1·60	1·2	1·3	2·3	1·64	2·0	1·5	1·5	1·49	1·6	1·5	1·4
Cannabis	0·99	0·9	2·1	0	1·51	1·9	1·7	0·8	1·50	1·7	1·3	1·5
Solvents	1·28	2·1	1·7	0	1·01	1·7	1·2	0·1	1·52	1·9	1·5	1·2
4-MTA	1·44	2·2	2·1	0	1·30	1·0	1·7	0·8	1·06	1·2	1·0	1·0
LSD	1·13	1·7	1·4	0·3	1·23	2·2	1·1	0·3	1·32	1·6	1·3	1·1
Methylphenidate	1·32	1·2	1·3	1·6	1·25	1·4	1·3	1·0	0·97	1·1	0·8	1·1
Anabolic steroids	1·45	0·8	2·0	1·7	0·88	1·1	0·8	0·8	1·13	1·3	0·8	1·3
GHB	0·86	1·4	1·2	0	1·19	1·4	1·1	1·1	1·30	1·4	1·3	1·2
Ecstasy	1·05	1·6	1·6	0	1·13	1·5	1·2	0·7	1·09	1·2	1·0	1·1
Alkyl nitrites	0·93	1·6	0·9	0·3	0·87	1·6	0·7	0·3	0·97	0·8	0·7	1·4
Khat	0·50	0·3	1·2	0	1·04	1·6	1·2	0·3	0·85	0·7	1·1	0·8

Table 3: **Mean independent group scores in each of the three categories of harm, for 20 substances, ranked by their overall score, and mean scores for each of the three subscales**

Figure 3. Mean Independent group scores in each of the three categories of harm, for 20 substances, ranked by their overall scores, and mean scores for each of three sub scales.

From: Nutt, D., King, L. A., Saulsbury, W., & Blakemore, C. (2007). Development of a rational scale to assess the harm of drugs of potential misuse. *The Lancet*, *369*(9566), 1047–1053.

CANNABIS AND PSYCHIATRIC DISORDERS (ANXIETY, DEPRESSION, AND RELATED MOOD DISORDERS)

Human studies on the effects of *Cannabis* on anxiety and depression or mood disorders include studies on THC, CBD, and whole plant material. Dosing consisted of a range between 5mg-30mg oral THC and a single clinical study looked at 0.5mg/kg THC for changes in mood and related behavior. For CBD, clinical studies examined oral doses ranging between 60mg-600mg and 1mg/kg for improvements in related mood disorders. Conversely blocking the active sites for THC with the CB_1 receptor antagonist, rimonabant is capable of increasing stress and anxiety levels at an oral dose of 70mg.

Anxiety and Mood Disorders

The effects of *Cannabis* on anxiety and depression may depend on the ratio of certain cannabinoids, the individual user, and the context in which it is used. One of the active ingredients of *Cannabis* can cause an acute and short-lasting episode of anxiety, which often resembles panic, in naïve users. For a naïve user, a dose of oral THC that is likely to start to induce anxiety is >5mg synthetic Δ^9-THC (for a man of average weight) and a higher dose could induce both panic attacks and paranoias[94]. However, the same is not necessarily true for all cannabinoid*s*.

In a study with 10 treatment-naïve patients with generalized social anxiety disorder, 400mg oral CBD was shown to reduce anxiety compared to placebo. This anxiolytic effect was associated with significantly reduced regional cerebral blood flow (measured by uptake of 740MBq of 99mTc-ECD) in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, while increasing cerebral blood flow (ECD uptake) in the right posterior cingulate gyrus[95]. Similarly, a study of 24 patients with social anxiety disorder found an association between CBD (600mg; n=12) and decreases in anxiety within the context of public speaking task[96].

In 1974, an interactive study between CBD and THC showed that CBD (60 mg), added to Δ^9-THC (30 mg), changed the symptoms induced by THC alone in such a way that the subjects receiving the mixture showed less anxiety and more pleasurable effects [97]. In 1982, a study confirmed a similar effect with CBD (1 mg/kg), co-administered with THC (0.5 mg/kg), and this combination also significantly reduced anxiety indices in healthy volunteers [98].

An early study on *Cannabis* use in Jamaica revealed no significant differences between a group of 30 users, and matched controls with respect to mood, thought, or behavior [99]. An international study funded by the National Institute on Drug Abuse, examined a group of 47 long-term hashish users in Greece. Differences in the number of users within defined psychopathology, as compared to controls was accounted for by "personality disorders," with more psychiatric abnormalities being observed in the moderate user group as compared to heavy users [100,101]. A few years later, another study documented that *Cannabis* users in Costa Rica believed that use helped with depression. No significant adverse effects, or development of adverse health effects resulting from *Cannabis* use were observed[44].

The effects of THC are not consistent and often may misrepresent the effects of whole *Cannabis*[102]. In a

study of oral THC, healthy volunteers received two doses of THC (7.5 and 15mg by mouth) or placebo, across separate sessions, before performing tasks assessing facial emotion recognition and emotional responses to pictures of emotional scenes[102]. In this three-session, double-blind, placebo-controlled study, THC significantly impaired recognition of facial fear and anger, marginally impairing recognition of sadness and happiness. The subjective responses to THC were not consistently positive – of the 25 study participants, 15 indicated a desire to take the 7.5mg dose again, whereas only 11 out of 25 did so at the higher 15 mg dose. Just over half of the participants identified THC as "marijuana-like" (7.5mg: 56%; 15mg: 52%). This study parallels many other findings on this subject – the paradox between dampened amygdalar reactivity and increased physiological indicators of emotional response remains a mystery to be resolved. The authors concluded that this property could potentially increase the appeal of *Cannabis* to certain users. As *Cannabis* use can lead to reduced sensitivity to anxiety-provoking emotional signals in some people, this may facilitate certain social interactions, especially amongst individuals with social inhibition or related disorders.

It has been well demonstrated that 'blocking' or interfering with CB_1 receptor signaling can increase anxiety. One study documented that the CB_1 receptor antagonist/inverse agonist, rimonabant, increases anxiety induced by public speaking in healthy humans. The anxiogenic effects occurred selectively during anticipatory and performance speech, without interfering with the pre-stress phase, meaning that the drug effects occurred selectively in response to an aversive situation[103].

Inhaled *Cannabis* and mucosal sprays – with precise amounts of key cannabinoid ingredients – do not induce the same side effects as pure THC controls[104]. Research suggests that a *Cannabis* "overdose" (i.e., anxiety, panic attack, etc.) can be treated (or prevented prophylactically) with foodstuffs such as pine nuts, lemons, basil and/or orange juice, as these foodstuffs share many relevant, pharmacologically active compounds[104].

Similar to the literature on the effects on *Cannabis* on anxiety, the effects of *Cannabis* on mood disorders are contradictory. For example, a group of authors published case reports suggesting *Cannabis* can cause an acute depressive reaction in those with underlying depression. However, their later case reports suggest *Cannabis* use can *improve* symptoms of bipolar disorders[31,101,105]. Cross sectional studies suggest that depression is associated with *Cannabis* use, and that *Cannabis* consumption is related to an increased risk of depression later in life[13,106]. Likewise for anxiety, it has been noted that "Frequent cannabis users consistently have a high prevalence of anxiety disorders and patients with anxiety disorders have relatively high rates of cannabis use [94]." It is unknown whether *Cannabis* use leads to a greater incidence of depression and anxiety later in life. In one survey, *Cannabis* use and depression were not associated once medical use was taken into account[107].

In some cases, an illness (and not the use of *Cannabis*) may be causative factor for depression. Though there is a modest increase of risk amongst problematic users of developing depression or an anxiety disorder later in life, a recent meta-analysis found that that small, but statistically significant association between *Cannabis* and anxiety hinged on the inclusion of a single study[108]. While *Cannabis* may provide some benefit to anxiety or depressive/mood disorders in some individuals, the true relationship between *Cannabis* use and anxiety and depressive disorders later in life remains unsubstantiated by current research. Similar to anxiety, differential effects of *Cannabis* on depression may be due to differences in

cannabinoid composition. Indeed, CBD has been shown to produce anti-depressant like effects similar to imipramine[109,110].

Suicide and Suicidal Ideation

Recent epidemiological work found no relation between the number of medical *Cannabis* users and completed suicides[111]. In fact, U.S. states that legalized the use of medical *Cannabis* were shown to have lower rates of suicide among men between the ages of 20 and 39, when compared to states that did not legalize medical *Cannabis* use[112].

Research among non-medical *Cannabis* using populations has received considerably more attention. Unfortunately, while some studies have shown associations between *Cannabis* use and heightened suicide ideation and attempts, a number of studies have either failed to control for confounds or, when they have, reported no association between *Cannabis* use and suicide[113-118] .

Post-Traumatic Stress Disorder

There has been a recent emergence of empirical studies on the effects of *Cannabis* for symptoms of Post-Traumatic Stress Disorder (PTSD), borne primarily out of the observation that individuals with PTSD report using *Cannabis* to cope with PTSD symptoms; specifically, hyperarousal, negative affect, and sleep disturbances[119-121]. Indeed, empirical work has consistently demonstrated that the endocannabinoid system plays a significant role in the etiology of PTSD, with greater availability of cannabinoid type 1 receptors documented among those with PTSD than in trauma-exposed or healthy controls[122,123].

B. THERE IS NO SIGNIFICANT DIVERSION OF THE DRUG OR SUBSTANCE FROM LEGITIMATE DRUG CHANNELS.

Currently available standardized preparations of *Cannabis* have been found to have a very low potential to be converted into controlled substances of abuse, and there is no supporting evidence of street markets existing for such psychoactive preparations[60]. Two examples of this are dronabinol and nabiximols. Dronabinol, an oral preparation of THC, is isolated from the *Cannabis* plant or synthetically produced. Nabiximols, a recently licensed *Cannabis* medicine, approved and available in 27 countries, contains equal amounts of THC and the synergistic non-intoxicating CBD. Dronabinol has also been proposed, and has demonstrated efficacy in limited trials, as a treatment for *Cannabis* use disorders[63]. There were no available peer-reviewed reports documenting a significant street market or conversion of medical *Cannabis* products distributed through pharmacies and dispensaries in Canada, U.S. Holland or from any other of the numerous countries that have *Cannabis* access programs, at the time this report was written.

Whole plant *Cannabis* strains that are inhaled can contain varying ratios of active constituents, and thus may vary in a range of effects, and may therefore have a higher potential for conversion into other controlled substances than dronabinol or nabiximols[64]. CBD also demonstrates a low abuse potential and has been shown to not enhance significantly the reinforcing effects of THC or positive subject effects of *Cannabis*[65].

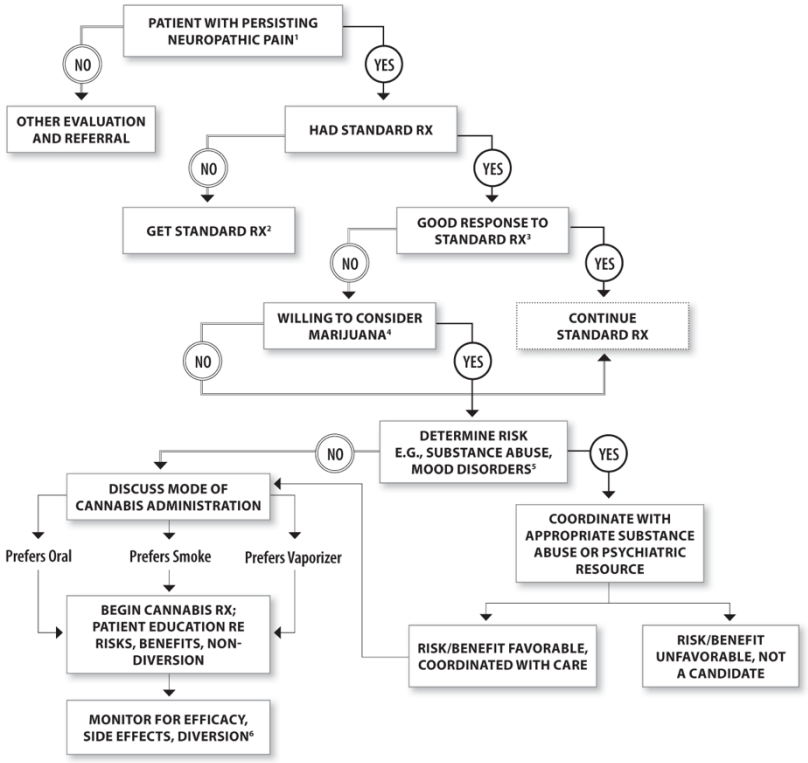
No cases of diversion of *Cannabis*-based medicines (Dronabinol, Sativex, Epidiolex, Rimonabandt, or *Cannabis* from NIDA's marijuana operation at the University of Mississippi) have been reported[60]. This reassuring profile is consistent with clinical experience of nabilone and dronabinol, which have been available by prescription for decades[66]. In summation, published research articles report abuse or diversion as "rare and isolated" and the street market for these psychoactive drugs was determined to be very low, if it exists[60,124].

C. INDIVIDUALS ARE NOT TAKING THE SUBSTANCE ON THEIR OWN INITIATIVE, RATHER ON THE BASIS OF MEDICAL ADVICE FROM A PRACTITIONER LICENSED BY LAW TO ADMINISTER SUCH SUBSTANCES.

More than 2 million Americans are registered to legally access medical *Cannabis* and its products in over 40 states with the supervision of a physician.

Physician Protocols for Medical Cannabis

Physicians and health care providers have recently begun to develop clear protocols for treating patients with *Cannabis*-based medicines. For example, the University of California Center for Medicinal Cannabis Research (CMCR) in the U.S., completed a series of randomized clinical trials with patients and has published their guidelines for medical care[125]. Additionally, the Harvard based TheAnswerPage.org online Continuing Medical Education (CME) program offers medical *Cannabis* training for physicians. These guidelines suggest that *Cannabis* therapeutics, like any other treatment mode, should be based on careful assessment of the patient's condition with consideration for other possible treatments. A possible treatment decision-tree for physicians, similar to those guidelines established by the Medical Board of California for doctors (using neuropathic pain as an example), is described below:



Physicians recommending medical *Cannabis* should:

1. Take a history and conduct a good faith examination of the patient.

2. Develop a treatment plan with objectives.

3. Provide informed consent, including discussion of side effects.

4. Periodically review the treatment's efficacy.

5. Obtain consultations, as necessary.

6. Keep proper records supporting the decision to recommend the use of medical *Cannabis*.

D. THE SUBSTANCE IS NOT SO RELATED IN ITS ACTION TO A SUBSTANCE ALREADY LISTED AS HAVING A POTENTIAL FOR ABUSE TO MAKE IT LIKELY THAT IT WILL HAVE THE SAME POTENTIAL FOR ABUSE AS SUCH SUBSTANCE, THUS IT IS NOT REASONABLE TO ASSUME THAT THERE MAY BE SIGNIFICANT DIVERSIONS FROM LEGITIMATE CHANNELS, SIGNIFICANT USE CONTRARY TO OR WITHOUT MEDICAL ADVICE, OR THAT IT HAS A SUBSTANTIAL CAPABILITY OF CREATING HAZARDS TO THE HEALTH OF THE USER OR TO THE SAFETY OF THE COMMUNITY.

Despite the increasing popularity of edible *Cannabis* products, no significant if any, diversion of existing cannabinoid drugs has ever been reported[60]. Guidelines are established for security and non-diversion of *Cannabis* grown in states with access programs. Dronabinol is a pure form of THC has a very low, if any, street value. And a significant black market for dronabinol may not exist, and instances of diversion are "rare and isolated" despite being available by prescription for decades[60].

FACTOR 2: SCIENTIFIC EVIDENCE OF THE PHARMACOLOGICAL EFFECTS AND GENERAL PHARMACOLOGY OF *CANNABIS*

We concur with the U.S. Food and Drug Administration's (FDA) response, in specific regards, to previous FDA 8 Factor petitions to reschedule *Cannabis*, that there is abundant scientific data available on the neurochemistry, toxicology, and pharmacology of marijuana. However, there is limited research of actual *Cannabis* plant material administered in animals in modern research, most so called marijuana or *Cannabis* in basic or animal research is conducted with dronabinol (a Schedule III drug). Hence, if THC or dronabinol is considered to be a form of marijuana or *Cannabis*, as has been suggested in previous DEA and FDA 8 Factor analysis responses, then this represents another reason *Cannabis* should be rescheduled.

[This section includes a scientific evaluation of marijuana's neurochemistry and pharmacology, central nervous system effects including human and animal behavior, pharmacodynamics of central nervous system effects, cognitive effects, cardiovascular and autonomic effects, endocrine system effects and immunological system effects. The overview presented below relies upon the most current research.]

Basic Pharmacology

Humans have used drugs derived from plants since time immemorial. For millennia, the opium poppy (Papaver somniferum) has been utilized to lessen pain and suffering and to produce euphoria[126]. Similarly, humans have used the *Cannabis* plant (Cannabis spp. Sativa, Indica, or Ruderalis) for thousands of years – to reduce pain, control nausea, stimulate appetite, control anxiety, and produce feelings of euphoria[127]. While the neurochemical systems that produce the effects of opiates are separate from those responsible for *Cannabis'* activity, both of these naturally occurring materials rely on a complex internal system of receptors and biochemical messengers to exert their effects on our brain and bodies. The science of a distinct "endocannabinoid" system is a relatively new discovery, which continues to reveal a remarkable number of comparatively safe therapeutic potentialities.

The first cannabinoid, cannabinol, was isolated in 1899 and its structure elucidated in 1940, but it was not until 1964 that THC [(-)-trans-Δ^9-THC isomer], the psychotomimetically active (primary euphoriant) substance in *Cannabis* – was isolated, and its structure and absolute configuration determined[128-132]. The cannabinoid compounds are derived from real cannabinoid compounds in the plant, cannabinoid acids. The first one, cannabidiolic acid, was isolated and identified by Krejčí and Šantavý in 1955[131,133,134]. Since the discovery of THC, researchers have made some compelling discoveries. These discoveries help us to better understand how and why *Cannabis* and cannabinoid-based medicines have proven to work so well, for so many diverse maladies[135]. The evidence that these substances have the potential to be medicinally useful is overwhelming[136-139].

Some of the therapeutic benefits of the *Cannabis* plant are derived from the interactions of its constituent cannabinoid molecules with the human body's own endocannabinoid system (ECS). The receptors of the ECS were discovered by Dr. William Devane in 1988[140]. After this discovery, Dr. Lumír Hanuš isolated endocannabinoids from mammalian brains[141-146]. The ECS modulates multiple and complex signaling pathways – a system responsible for regulating a variety of key physiological processes including movement, mood, memory, appetite, and pain[142].

One of the world's leading cannabinoid researchers, Dr. Ethan Russo, offers this comprehensive description of the ECS and its importance to a variety of physiological functions:

> *"The analgesic and palliative effects of the cannabis and cannabinoid preparations have been amply reported over the past generation...." In essence, the effects result from a combination of receptor and non-receptor mediated mechanisms. THC and other cannabinoids exert many actions through cannabinoid receptors, G-protein coupled membrane receptors that are extremely densely represented in central, spinal, and peripheral nociceptive pathways. Endogenous cannabinoids (endocannabinoids) even regulate integrative pain structures such as the periaqueductal gray matter. The endocannabinoid system also interacts in numerous ways with the endogenous opioid and vanilloid systems that can modulate analgesia, and with a myriad of other*

> *neurotransmitter systems such as the serotonergic, dopaminergic, glutamatergic, etc., pertinent to pain. Research has shown that the addition of cannabinoid agonists to opiates enhances analgesic efficacy markedly in experimental animals, helps diminish the likelihood of the development of opiate tolerance, and prevents opiate withdrawal. Researchers have suggested that a clinical endocannabinoid deficiency may underlie the pathogenesis of migraine, fibromyalgia, idiopathic bowel syndrome, and numerous other painful conditions that defy modern pathophysiological explanation and lack adequate treatment[147]."*

More than 20 years since researchers began developing an understanding of the ECS, two types of cannabinoid receptors – CB_1 and CB_2 – have been identified, setting the stage for discoveries that have dramatically increased our understanding of how *Cannabis* and its many constituent cannabinoids affect the human body[148,149]. CB_1 receptors are found predominantly in the central nervous system, particularly in the brain, and in organs and tissues such as the eyes, lungs, kidneys, liver, and digestive tract[66]. The brain's receptors for cannabinoids far outnumber the presence of all other neurotransmitter receptors combined. The relative safety of *Cannabis* is, at least in part, explained by the fact that these otherwise numerous cannabinoid receptors are virtually absent from those regions of the brainstem responsible for vital functions such as breathing and heart control. In comparison, CB_2 receptors are primarily located in tissues associated with immune function, including the spleen, thymus, tonsils, bone marrow, and white blood cells[66]. *Cannabis* compounds such as CBD also interact with non-cannabinoid serotonin (i.e., $5HT_{1A}$) and adenosine (i.e., A_2A) receptors[67,78,150-154]. There are a number of orphan receptors that are recognized as novel therapeutic targets that also appear to play a role in *Cannabis* pharmacology[155-159].

Ongoing research is helping scientists and physicians to increasingly understand the crucial role of the ECS in regulating a variety of key bodily functions. As best noted by the researcher who first isolated and identified THC – Dr. Raphael Mechoulam – the discovery of the ECS has generated a great deal of interest in identifying opportunities for the development of a wide variety of *Cannabis*-based and synthetic cannabinoidergic therapeutic drugs[160-162].

Central Nervous System Effects

THC increases the metabolic rate in the brains of humans and other mammals[163]. Most cannabinoid effects are mediated by cannabinoid receptors, their distribution reflects many of the medical benefits and side effects in this eight-factor analysis. To name a few, cannabinoids can have analgesics effects, muscle relaxant effects, enhance appetite, and hormonal actions. Neuroprotective properties of different cannabinoids (i.e., THC and CBD in ischemia and hypoxia are examples of some well-known receptor-independent actions of cannabinoids.

Cannabinoids interact with a number of neurotransmitters and neuromodulators, such as acetylcholine, dopamine, gamma-aminobutryic acid (GABA), histamine, serotonin, glutamate, norepinephrine, prostaglandins and the endorphin (opiate) system. A number of pharmacological effects of *Cannabis* can be explained on the basis of such interactions. For example:

- Tachycardia and hypo-salivation with dry mouth are mediated by the effects of THC on acetylcholine activity[164,165].
- Anti-emetic properties are due, in part, to interactions with serotonin[166,167].
- Hypomotility and sedation from *Cannabis* are in part due to interactions involving acetylcholine, GABA, and prostaglandins.
- Therapeutic effects in movement and spastic disorders are due to interactions involving GABAergic, glutamergic, and dopaminergic transmitter systems[126]

Human Behavioral Effects

In many species a mixture of depressant and stimulant effects in the CNS characterizes the behavioral effects of THC. In humans, THC intoxication is usually noted as a pleasant and relaxing experience[168]. Occasionally, unpleasant feelings are reported such as anxiety, which may escalate to a panic attack. A sense of enhanced well-being may alternate with dysphoric phases. *Cannabis* improves taste responsiveness and enhances the sensory appeal of food[169]. *Cannabis* or THC may induce sleep.

Adverse effects of medical *Cannabis* are within the range of effects tolerated for other medications[170,171]. It is has never been convincingly demonstrated that heavy *Cannabis* use impairs cognition outside of acute intoxication. Long-term medical *Cannabis* use is reported to be well-tolerated without significant physical or cognitive impairment[40,47,52,57,172]. Acute THC intoxication impairs learning and memory, and can adversely affect psychomotor and cognitive performance. Neuropsychological performance can be impaired from intoxication but after cessation of use these effects are normalized without signs of residual behavioral effects[40].

Cardiovascular

Historically *Cannabis* has been used as a treatment for a number of ailments such as atherosclerosis, cardiac palpitations, and hypertension[173]. This suggests the involvement of the cardiovascular (CV) system, and since the 1970's the effect of *Cannabis* and the cannabinoids on the CV system has been studied intensively[21,174-176].

In vivo THC can cause a decrease in blood pressure and heart rate in anesthetized mammals, and an increase in blood pressure and decrease in heart rate in conscious animals. In humans there is an acute increase in heart rate, but variable effects on blood pressure. The effects of THC are largely through the CB_1 receptors, which mediate the activity of the autonomic nervous system.

In vitro observations have documented that vasorelaxation can be caused by the phytocannabinoids THC, CBD, CBN, and THCV and vasoconstriction can be caused by THC and THCV[177-184]. Vasorelaxation by THC is mediated by prostaglandins, activation of sensory nerves, ion channel modulation, and activation of PPAR-gamma. Vasoconstriction from THC is mediated by prostanoids, CB_1 receptors, and sympathetic

stimulation; THC can inhibit the vasorelaxation caused by sensory nerve activation from acetylcholine, bradykinin, and anandamide. One study in human arteries suggests that CBD may cause vasorelaxation by activating TRPV1, nitric oxide, and allosterically modulating CB_1 receptors[181].

A 2016 study on the cardiovascular effects from the abrupt cessation of long-term *Cannabis* use in humans showed no significant changes between groups[185]. The authors conclude, *"In the presented post-hoc analysis, no significant changes in heart rate, blood and pulse pressure were found after abrupt cessation of long-term daily cannabis smoking, which stands in contrast especially to the results of the study of Vandrey et al., who found significant increases in blood pressure and slight increases in the heart rate of their sample*[185]."

Respiratory

Unlike opiates, *Cannabis* compounds, such as THC, do not depress respiration and cannot depress respiratory drive due to sparse receptor density in medullary respiratory centers of the human brain[34,35]. Pulmonary issues associated with *Cannabis* smoking include chronic bronchitis, particularly chronic cough, and sputum production, with more variable effects on wheezing and generally negative effects on breathlessness. Reducing *Cannabis* use often leads to a resolution of these symptoms. Reducing or quitting *Cannabis* smoking was associated with reductions in the prevalence of cough, sputum and wheeze to levels similar to nonusers[186]. However, these issues are avoidable by using vaporizer/volatilizer technology or alternative routes of administration[79,80]. Importantly, lifetime use of *Cannabis* smoking is not associated with an increase incidence of lung cancer[81].

Cannabis has been documented to treat symptoms of certain airway ailments such as asthma. Bronchodilatory effects of orally administered dronabinol were not found in asthmatic patients although such effects of inhaled THC had been shown[187-189]. For example, a case report from Costa Rica documents the study of two children with asthma, one treated the ailment by smoking *Cannabis,* while the other child abstained and succumbed to the disease[44].

Endocrine Systems

The earliest systematic studies of *Cannabis* and the compounds found on the plant, focused on the effects on mood, anxiety, and the endocrine system[190]. The effects of *Cannabis* on mood and anxiety disorders have already been covered earlier in this document, this section will focus on the effects of *Cannabis* and related compounds on endocrine systems known to be stress responsive and otherwise contribute to mood and related disorders.

The dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis is common etiology or underlying mechanism in humans with major depression[191]. Conceptually the hyperactivity of the HPA axis

accompanies depression, hence attenuating hyperactivity of the HPA axis is a common feature of targeted therapies for related depression and mood disorders. The inability to control or suppress the release of cortisol is a considered diagnostic of mood disorders related to the HPA axis.

In naïve or infrequent users, *Cannabis* or THC can increase the secretion of cortisol, while regular or chronic *Cannabis* users demonstrated an attenuation of this effect, perhaps representing the development of tolerance[192,193]. Additionally, clinical research has confirmed an inhibition of stress-induced activity of the HPA axis in adult and adolescent *Cannabis* users[194,195]. CBD has been demonstrated to stimulate the HPA axis, attenuating the diurnal decline in cortisol levels[196].

Preclinical and basic research of the effects of cannabinoids on the HPA axis has demonstrated that the work in mammalian species parallels the effects in humans. To summarize the animal and human research, the data demonstrate that *Cannabis* and cannabinoids can increase HPA axis activity via the monoaminergic hindbrain nuclei, while the inhibitory effects on cortisol (stress hormone) secretion is due to direct actions on limbic and hypothalamic circuitry.

Research has investigated the effects of *Cannabis* on the hypothalamic-pituitary-thyroid (HPT) axis. Disorders of the HPT axis are associated with depressed mood in adults and cognitive deficits acquired during development. In humans who regularly use *Cannabis* found that thyroid hormones vital for proper development and metabolic regulation, were within normal limits and did not correlate with concentrations of THC or its major metabolites[197].

Growth hormone, or somatotropin, is an anabolic hormone that stimulates growth and regulates energy homeostasis. Prolonged and heavy administration of more than 200mg of THC a day in human males can decrease serum growth hormone concentrations that are evoked by insulin (a gold standard test for growth hormone activity) [198]. The effects of smaller doses of THC have not been reported to have significant effects on growth hormone release. This suppression of growth hormone release has not been reported in any clinical trial of *Cannabis* or its products.

The pineal gland synthesizes melatonin during the night and plays an important role in the sleep wake cycle in mammals. A study of THC on melatonin secretion in human subjects found that 10mg of THC administered by smoking when melatonin concentrations low, can produce a 30-fold increase in melatonin 1-2 hours post smoking[199]. However, in the same study one of subjects had very high basal melatonin level and THC administration reduced the concentration of melatonin in this individual. Increases in melatonin concentrations, such as those that are often observed hours after *Cannabis* use, contribute to sleep.

The effects of the phytocannabinoids on the HPA axis and reproductive hormones are well described in human and preclinical studies. More of research is needed in the areas of growth hormone and melatonin in light of findings that cannabinoids can beneficially alter the activity of these hormones.

Immune System

THC and CBD converge to inhibit immune functional activities by altering the production of pro-inflammatory cytokines and chemokines. The common mode of action between THC and CBD causes a switch from the production of Th1 cytokines such as IFN-gamma, TNF-alpha, IL1Beta, and IL-2 to that of Th2 cytokines such as IL-10 and IL-4[200,201]. THC and CBD have anti-inflammatory effects and can beneficially inhibit the migration of immune cells[201-204]. THC, CBD, and *Cannabis* have a documented ability to alter the functioning of the immune system but a role in increasing susceptibility to infection and/ or disease progression in humans has failed to reach a significant association in many studies[174,205-207].

FACTOR 3: THE STATE OF CURRENT SCIENTIFIC KNOWLEDGE REGARDING THE DRUG OR OTHER SUBSTANCE

Chemistry

Cannabinoids are a class or group of related compounds consisting of more than a hundred terpenophenolic compounds (currently 144 have been documented), most commonly associated with the pharmacological activity of *Cannabis*. Cannabinoids mainly exist in the *Cannabis* plant as carboxylic acids and are converted to neutral analogs by light and heat while in storage or when combusted[208]. The alkyl group at the third carbon atom is considered an important site in substrate-receptor interactions[208,209]. This group is typically a pentyl – for example, in Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabigerol (CBG), cannabidiol (CBD), and cannabinol (CBN) – but can also be a propyl, in which case the compounds are named by attaching the suffix -varin to the name of the pentylated analog, e.g., tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabigerovarin (CBGV), and cannabivarin (CBNV) – butyl (THC-C4, CBD-C4, and CBN-C4) or methyl (tetrahydrocannabiorcol, cannabidiorcol, and cannabiorcol).

Cannabis plants typically exhibit one of the three main distinctly different chemotypes based on the absolute and relative concentrations of Δ^9-THCA, CBD, and CBN (after conversion from the respective acids). Some researchers refer to these as THC or drug-type, intermediate type, and fiber-type[21,210]. Plants with more rare chemical profiles have been established, including those predominant in CBG or THCV, and those lacking any cannabinoids, for a total of five general types[211,212]. The mean content of Δ^9-THC, (including Δ9-tetrahydrocannabinolic acid [Δ^9-THCA]), in the THCA-predominant plant material has been increasing in the past few decades, due to changes in cultivation techniques and selective breeding.

The cannabinoid profile is affected most by the plant's sex, genotype, and maturity followed by environmental and other factors, such as light intensity, light cycle, temperature, and fertilization[213,214]. Cannabinoids are produced in glandular trichomes distributed across all epidermal surfaces of the plant's aerial parts at varying degrees. The distribution of glandular trichomes and, hence, phytocannabinoids varies widely, from the lowest concentrations found in stems to increasing amounts in

large leaves, subtending leaves of the inflorescences, and to the highest concentrations found in female flower bracts.

Cannabinoids are highly lipophilic, permeate cell membranes, and have the ability to cross the blood-brain barrier both when inhaled (i.e., vaporized or smoked) and ingested.

Human Pharmacokinetics

The best-studied pharmacokinetics of a substance from *Cannabis* is THC[215]. The pharmacokinetic profiles of CBD and CBN are somewhat similar to that of THC. No significant differences in the pharmacokinetics of women and men have been found. Values for clearance average about 0.2 L/kg-hr, but are highly variable due to the complexity of cannabinoid distribution

Metabolism

The metabolism of THC is complex, the route of administration affects the quantitative profile of metabolites, and this is well studied in a number of different species[216-220]. The inter-species differences may in part be responsible for some problems of extrapolating of pharmacological and toxicological data.

More than 100 metabolites for THC have been identified, including di- and tri- hydroxyl, ketone, aldehyde, and carboxylic acid THC metabolites. THC metabolizes primarily to 11-OH-THC, THCCOOH and associated glucuronide conjugates. The liver is the primary site of cannabinoid metabolism, and to a much lesser extent the brain, intestine, and lung are other tissues metabolize phytocannabinoids[221-223].

11-OH-THC is a potent, primary metabolite that is produced by the C9 hydroxylation of THC by liver/hepatic cytochrome P450,2C9, 2C19, and 3A4 enzymes. Early literature on the subject originally proposed that 11-OH-THC was the main psychoactive analyte. 11-OH-THC is produced in equal amounts to orally administered THC, but only about 10% of THC is metabolized in this way when inhaled. 11-OH-THC conjugates with fatty acids are proposed to be the main form of THC storage within tissue[224].

The concentrations THCCOOH rise above that of THC in the plasma about 30minutes after inhalation and about 1 hour after oral administration. THCCOOH-glucuronide is a more water-soluble metabolite, it is readily excreted, the major metabolite in blood and plasma, can be detected in the blood for many hours and is considered to be the principal Phase II metabolite[225-227].

THC metabolizes to equipotent 11-hydroxy-THC (11-OH-THC) and inactive 11-nor-9- carboxy-THC (THCCOOH) metabolites during *Cannabis* smoking. “For inhalation, peak concentrations for THC were observed 8 minutes (range 6–10 minutes) after 1st inhalation, whereas 11-OH-THC peaked at 15 minutes (range 9–23 minutes) and THC-COOH at 81 minutes (range 32–133 minutes)[228].” The ratio of THC to 11-OH-THC declines and reaches a 2:1 ratio around 2-3 hours.

After oral administration, much higher amounts of 11-OH-THC are formed than with inhalation or intravenous administration[229-232]. In several clinical studies the plasma levels of 11-OH-THC exceed THC concentrations after oral administration[175,232-234].

Many metabolites of CBD have been discovered but the two primary metabolites are 7-OH-CBD and 7-oic acid[235,236]. The 7-oic acid and its hydroxylated derivatives are abundant in human urine and feces[216].

The primary metabolite of CBN is monohydroxy CBN, with 7-OH metabolite being the most abundant in the milleui[220,235,237-239]. The metabolic profile of CBD is less complex than that of THC or CBD.

A significant first pass liver effect occurs only with oral administration.

Distribution

Plasma THC levels rapidly decrease as this highly lipophilic compound is easily distributed through vascular tissue and metabolized in the liver[240]. Shortly after administration significant concentrations of cannabinoids are found in sites such as body fat (long-term storage), liver, heart, lung, gut, kidney, spleen, mammary gland, placenta, adrenal cortex, thyroid, and pituitary gland.

Excretion

Eighty percent of THC is excreted through feces. Only traces are secreted through urine. The dominant urinary metabolite is THC-COOH-O-glucuronide, 50% is excreted within the first day after administration.

CBD shows a similar excretion profile with acids and glucuronide conjugates dominating the profile.

A single dose of CBN was excreted in urine within 72 hours.

Absorption and Bioavailability

In this sections below, various routes of absorption and bioavailability are reviewed.

Inhalation

A rapid absorption occurs after the inhalation of smoked or vaporized *Cannabis*[168]. THC can be detected in plasma within seconds after the first inhalation but absorption from the lungs reaches peak concentrations in about 3-8 minutes. It is estimated that between 15-50% of the cannabinoids, such as

THC, reach systemic circulation due to: loss by pyrolysis (30%), loss to side stream smoke (10-30%), and incomplete absorption and metabolism in the lung. Bioavailability also depends on inhalation topography, such as the depth of inhalation, duration of inhalation, and length of holding the inhalation in the lungs. Generally, the bioavailability of inhaled THC is considered to be approximately 25%, with large intra- and inter-subject variability due to many factors including inhalation topography[241,242]. The bioavailability of THC is much greater than that from oral administration.

A systemic bioavailability for the inhalation of THC can be greater for participants of clinical studies that have previous experience with *Cannabis.* In one study regular *Cannabis* users demonstrated a bioavailability of THC of 23 +/-16% vs 10 +/-7% for occasional users[243]. Similarly, another study found the bioavailability of inhaled THC to be 27 +/-10% for the regular users and 14 +/-1% for the light or occasional users[244]. This data also suggests that through inhalation, experienced users can titrate their dose.

Bioavailability of inhaled CBD is 31 +/-13% and for CBN this approximately is 38%. CBD and CBN are often not detected 1 hour after inhaled administration, detection of CBD and CBN may be an indicator of recent use[225].

More efficient *Cannabis* inhalation delivery systems are being developed. Medical devices such as vaporizers have demonstrated to be more efficient, reducing side stream smoke, reducing production of harmful by-products related to combustion, and are also associated with avoiding any harmful effects related to smoking (i.e., bronchitis and airway irritation)[245-247].

After 16 and 30 mg inhaled THC, plasma concentrations reached 7.0 ± 8.1 and 18.1 ± 12.0 micrograms/L following one inhalation with mean (range) or maximal concentration of 84.3 (range 50–129) and 162.2 micrograms/L (76–267), respectively[248].

Plasma THC concentrations remain greater than 1 ug/L for at least 1 day after cessation of either daily *Cannabis* smoking or multiple oral THC doses.

Oral Administration

Oral administration of pure THC is slow, unpredictable and erratic; absorption is lower with delayed peak concentrations, and in some individuals two (and possibly more) THC metabolite peaks appear over time[168,249-252]. These two peak THC concentrations that appear after ingestion are possibly due to enterohepatic recirculation. Systemic bioavailability of dronabinol (marketed as Marinol) was only 10% as measured as a result of the extensive first-pass liver metabolism. Generally, maximal plasma concentrations can be reached 60-120 minutes after administration. However, in several studies peak plasma concentrations were observed as late as 4 to 6 hours after administration[168,230,253].

Absorption from oral administration is affected by the dose, vehicle (i.e., administering THC in sesame oil improves bioavailability), and physiological factors such as metabolism and excretion rates, ultimately influencing drug concentrations.

An extensive first-pass liver metabolism further reduces the oral availability of THC and other cannabinoids. THC is metabolized before it reaches the sites of action when taken orally. For example, 20mg of THC in food (chocolate cookie) and administration of dronabinol resulted in very low bioavailability after 1-5 hours, of 6 +/-3% or 7+/-3%, respectively. Peak plasma concentrations for the THC in food were reported as 4.4-11ug/L 1-5 hours about ingestion. Plasma THC concentrations remain greater than 1 ug/L for at least 1 day after cessation of either daily *Cannabis* smoking or multiple oral THC doses.

There are also high inter-individual variations with cannabinoid metabolism.

Opthalmic Administration

An ophthalmic administration study in animals demonstrated a bioavailability of THC, formulated with mineral oil, to vary between 6-40%[254]. Peak plasma concentration were reached after 1 hour and remained at significant levels for hours.

Sublingual Administration

Cannabis extracts can be administered sublingually, absorbed through the muscosa, to avoid first-pass metabolism by the liver. This results in low plasma levels of THC and CBD metabolites compared to inhalation, which resembles oral administration's pharmacokinetic profile.

Dermal Administration

The permeability of THC must be increased to result in significant concentration in the blood of mammals. In rats, a stable THC isomer was formulated with water, oleic acid, propylene glycol, and ethanol[255,256]. Studies examining or developing transdermal delivery of cannabinoids have found the mean effective permeability of coefficient for THC (in propylene glycol) of 6.3×10^{-6} cm/hour[168].

Rectal Administration

Rectal formulations absorption is lower but more consistent than oral formulation. The THC ester (hemisuccinate) suppositories demonstrated a bioavailability of 50%[229].

Plasma Levels vs. Administration Routes

Plasma profiles are similar for inhalation and injection while oral and sublingual administration share similar pharmacokinetic profiles. THC plasma maxima in the range of 100-250 ng/ml are measured after smoking 1gram of *Cannabis* with 1.75% and 3.25% THC. These plasma levels are significantly lower for sublingual administration.

Medical Uses for Marijuana/Cannabis

There is a wealth of clinical information available on the uses of standardized medical *Cannabis* products. The FDA has approved new drug applications for *Cannabis.* For example, a CBD-rich extract (Marketed as Epildiolex) is an imported, purified *Cannabis* extract that has been approved for clinical use in children and is currently in clinical practice across several institutions in the U.S. Additionally, an inhaled *Cannabis* study has recently been approved for investigating therapeutic effects in PTSD. At the time of writing this document, according to clinicaltrials.gov, there are hundreds of approved human research studies. These studies are currently either completed, recruiting, approved, or in process. A total of 144 are approved for THC, 96 are approved for CBD, and 559 are approved for marijuana or *Cannabis.* Due to Schedule I status, medical *Cannabis* preparations such as nabiximols and CBD-rich extracts are imported and cannot be manufactured in the U.S., even though they are licensed pharmaceutical products.

Whereas research in the U.S. has been historically restricted by a prevailing Federal prohibition on *Cannabis* and cannabinoids in the past, recent global discoveries have driven interest amongst scientists to investigate the now more than 100 different cannabinoids thus far identified on the *Cannabis* plant. Entire organizations have emerged, dedicated to basic medical and clinical research on the cannabinoid molecules. The International Cannabinoid Research Society (ICRS), formally incorporated as a scientific research organization in 1991, holds an annual international research symposia, and since its inception, the membership has more than quadrupled (www.icrs.co). The International Association for Cannabinoids as Medicine (IACM), founded in 2000, publishes a bi-weekly newsletter and holds a biennial symposium to highlight emerging clinical research concerning *Cannabis* therapeutics (www.cannabis-med.org). The University of California established the Center for Medical Cannabis Research (CMCR) in 2001 to conduct scientific studies to ascertain the general medical safety and efficacy of *Cannabis* products.

In 2010, the CMCR issued a report on the 14 clinical studies it has conducted, most of which were FDA-approved, double-blind, placebo-controlled clinical studies that demonstrated that *Cannabis* can control pain – in some cases better than all available alternatives[125]. More recently, the International Cannabis and Cannabinoid Institute (ICCI) was founded in the Czech Republic[257]. The goal of ICCI will be to identify, coordinate, and support global research priorities for the advancement of *Cannabis* and cannabinoid treatments through a multidisciplinary evidence-based approach that incorporates innovative tools and approaches (www.icci.science). Each of these international research organizations is dedicated, at least in part, to properly controlled, methodological scientific exploration into the therapeutic potential of *Cannabis* and the cannabinoids.

Emerging Clinical Data

To date, more than 30,000 modern peer-reviewed scientific articles on the chemistry and pharmacology of *Cannabis* and the cannabinoids have been published, and more than 1,500 articles investigating the body's natural endocannabinoids are published every year. In recent years, modern gold-standard placebo-controlled human trials have also been conducted.

A 2009 review of clinical studies conducted over a 38-year period found that "nearly all of the 33 published controlled clinical trials conducted in the U.S. have shown significant and measurable benefits in subjects receiving the treatment[148]." The review's authors made particular effort to note that cannabinoids have the capacity for analgesia through neuromodulation in ascending *and* descending pain pathways, neuroprotection, and by anti-inflammatory mechanisms – all of which indicate that the cannabinoids found in *Cannabis* have applications in significantly managing chronic pain, muscle spasticity, cachexia, and other variously debilitating conditions.

Currently, *Cannabis* is most often recommended as a complementary or adjunctive medicine. However, there exists a substantial consensus amongst experts in the relevant disciplines – including the American College of Physicians – that *Cannabis* and cannabinoid-based medicines have undeniable therapeutic properties that could potentially treat a variety of serious and chronic illnesses. What follows is a brief, annotated compilation of the emerging clinical data in support of the therapeutic usefulness of the cannabinoids.

Cancer

Cancer patients undergoing radiation and/or chemotherapy often suffer from significant nausea, pain, and other unpleasant side effects of their treatment. The effects of oral THC and mixed cannabinoid administration has been studied in more than 35 clinical trials for the treatment of chemotherapy-induced nausea and vomiting, and more than 40 clinical studies have looked at appetite modulation by cannabinoids. Years before any U.S. State authorized the medical use of *Cannabis*, a 1991 Harvard Medical School study revealed that nearly *half* (44%) of U.S. oncologists were recommending *Cannabis* to their patients as a way of mitigating side effects associated with cancer treatment[258].

In its 1999 review, the Institute of Medicine (IOM) concluded that *Cannabis* could be a valid, safe medicinal alternative for many people living with cancer[259]. Specifically, the IOM notes state, "In patients already experiencing severe nausea or vomiting, pills are generally ineffective, because of the difficulty in swallowing or keeping a pill down, and slow onset of the drug effect[260]." Cannabinoid medicines are both safely, and somewhat easily, formulated into both inhalable and suppository formats.

Since the release of the IOM report, new research has been published which clearly supports the use of *Cannabis* and the cannabinoids to curb the debilitating effects of cancer treatments. In 2001, a review of clinical studies of individuals with cancer, conducted in several U.S. states spanning multiple decades, revealed that inhaled cannabinoids and oral cannabinoids (in 591 and 1,281 subjects, respectively) were significantly effective anti-emetics versus the nausea and vomiting of chemotherapy[261]. Other studies have come to similar conclusions – that the active components in *Cannabis* produce palliative effects in cancer patients by preventing nausea, vomiting, and pain while stimulating appetite.

Beyond these palliative effects, the tumor-fighting properties of the cannabinoids have also been demonstrated in numerous pre-clinical studies, withstanding a successful Phase I clinical study looking at the safety of THC in patients with recurrent brain cancer. Researchers have observed that "these compounds [are] shown to inhibit the growth of tumor cells in culture and animal models by modulating key cell-signaling pathways. Cannabinoids are usually well tolerated, and do not produce the generalized

toxic effects of conventional chemotherapies[262]."

Combating Nausea and Vomiting Induced by Chemotherapy

Cannabis is used most often to combat the nausea and vomiting induced by chemotherapeutic agents, as well as pain caused by various cancers. More than 35 human clinical trials have sought to examine the effects of phytocannabinoids or synthetic cannabinoids on nausea, including several U.S. state-sponsored trials that took place between 1978 and 1986[258,263]. In reviewing this literature, scientists have concluded that, "THC is superior to placebo, and equivalent in effectiveness to other widely-used anti-emetic drugs, in its capacity to reduce the nausea and vomiting caused by some chemotherapy regimens in some cancer patients[263]."

A 1998 review by the British House of Lords Science & Technology Select Committee concluded, "cannabinoids are undoubtedly effective as antiemetic agents in vomiting induced by anti-cancer drugs. Some users of both find *Cannabis* itself more effective[264]." The House of Lords review was built upon data provided in a 1997 inquiry by the British Medical Association that further determined that natural *Cannabis* is, in some cases, more effective than synthetic THC (i.e. dronabinol)[265].

Previous clinical work has shown that orally administered synthetic cannabinoids (nabilone and dronabinol) are superior to dopamine receptor antagonists in preventing chemotherapy-induced nausea and vomiting. Until recently, there was not adequate information available on the tolerability of an acute dose titration of a standardized whole-plant *Cannabis* medicine; the results of clinical work suggest that rapid titration of a standardized *Cannabis* medicine appears to be well tolerated by most patients and efficacious in reducing the incidence of delayed nausea and vomiting[175,266].

Antineoplastic Actions of Cannabinoids

Recent scientific advances in the study of the endocannabinoid system have yielded exciting new leads for potentially groundbreaking anti-cancer treatments. In the past decade, preclinical studies, conducted both *in vivo* and *in vitro*, have demonstrated that different cannabinoids might have a remarkable effect in fighting different types of cancer cells. To date, studies have shown that cannabinoids arrest many kinds of cancer growths, both through the promotion of apoptosis (a.k.a. programmed cell death) and by arresting angiogenesis (blocking increased blood vessel production). Cannabinoids have also been shown to halt the proliferation, or spread, of cancer cells in a wide variety of cancer types. Unlike conventional chemotherapy treatments – that work by creating a toxic environment in the body, and are frequently responsible for compromising overall health – cannabinoids have been shown to selectively target tumor cells, leaving healthy surrounding cells undisturbed.

Cannabinoids and Tumor Reduction

The direct anti-tumor and anti-proliferation activity of cannabinoids, specifically CB_1 and CB_2 agonists, have been demonstrated in dozens of studies across a range of cancer types, including brain (gliomas), breast, liver, leukemic, melanoma, pheochromocytoma, cervical, pituitary, prostate, and bowel[262,267-285]. Evidenced anti-tumor activity has led to regression of tumors, reductions in both

vascularization (blood supply) and metastases (secondary tumors), as well as the direct destruction of cancer cells (apoptosis) in laboratory animals and *in vitro* human tissues[286-289]. A 2009 review of recent studies on the role of cannabinoids and cannabinoid receptors in the treatment of breast cancer notes that research on the complex interactions of endogenous cannabinoids and receptors is leading to greater scientific understanding of the basic mechanisms by which *all* cancers develop[268,287].

Cannabinoids have been shown to inhibit tumor growth in laboratory animals in multiple studies [268,290,291]. In one study, injections of synthetic THC eradicated malignant brain tumors in one-third of treated rats, and prolonged lifespan in another third by as long as six weeks. Other research on pituitary cancers suggests that cannabinoids may be the key to regulating human pituitary hormone secretion [292,293].

Research published in 2009 found that the non-intoxicating cannabinoid, CBD, inhibits the invasion of both human cervical cancer and human lung cancer cells. By manipulating CBD's up-regulation of a tissue inhibitor, researchers may have revealed the mechanism behind CBD's tumor-fighting effects[294]. A further *in vivo* study demonstrated "a significant inhibition" of lung cancer metastasis in mice treated with CBD[295]. The mechanism of the anti-cancer activity of CBD and other cannabinoids has been repeatedly demonstrated in both breast and brain cancers[296-299].

The anti-tumor effects of the cannabinoid THC on cholangiocarcinoma cells, an often-fatal type of cancer that attacks the liver's bile ducts, has also been evidenced. A 2009 study found that "THC inhibited cell proliferation, migration and invasion, and induced cell apoptosis." Interestingly, at low concentrations, THC reduced both the migration and invasion of cancer cells, while at high concentrations, THC triggered cell-death in tumors. In short, THC both reduced the *activity* and the *number* of cancer cells[281].

Research on cannabinoids and gliomas – a type of aggressive brain cancer for which there is no known cure – holds true promise for future treatments of this devastating disease. A study that examined both animal and human glioblastoma multiforme (GBM) tumors, the most common and aggressive form of brain cancer, describes how cannabinoids minimize gliomal growth by regulating the blood vessels that supply the tumors[300]. In another study, researchers demonstrated that the administration of CBD significantly inhibits the growth of subcutaneously-implanted 87 human glioma cells in mice[294]. The authors of the study noted that CBD *alone* was capable of producing a significant antitumor effect, both *in vitro* and *in vivo*, thus suggesting a possible application of CBD as a viable antineoplastic agent in humans.

The targeted effects of cannabinoids on GBM were further demonstrated in 2005 by researchers who showed that the cannabinoid THC both selectively inhibited the proliferation of malignant cells and induced them to die off, while leaving healthy cells unaffected [25]. While CBD and THC have each been demonstrated to possess tumor-fighting properties in isolation, research published in 2010 shows that the molecules work better in combination, as CBD *enhances* the inhibitory effects of THC on GBM cell proliferation and survival[301]. More recent work in mice has confirmed this enhancing effect of CBD on THC in cancer cells in animals. The research also tested a THC/CBD combination with and without chemotherapy in the animals. The research showed that combinations of *Cannabis* compounds can significantly improve the effect of the chemotherapy agent temozolomide[291].

Similarly, researchers have demonstrated in the last few years the mechanism by which cannabinoid and cannabinoid-like receptors in brain cells regulate these cells' differentiation, functions, and viability. This is suggestive evidence that cannabinoids – and other drugs that target cannabinoid receptors – might manage neuroinflammation and thus eradicate malignant astrocytomas, a type of cancer [268,302-304]. Such recent studies confirm the positive findings of earlier studies indicating the effectiveness of cannabinoids in fighting gliomas, some of the deadliest known forms of brain cancer[267,305-307].

The potential of cannabinoids to fight cancer in humans has also been seen in three recent large-scale population studies. These studies were originally designed to find correlations between smoked *Cannabis* and cancers of the lung, throat, head, and neck. Rather, researchers discovered that the cancer rates of *Cannabis* smokers were, at worst, seen in no greater prevalence than in those that smoked nothing at all – and many fared significantly better[81]. Results of this study suggested that cannabinoids might actually have a prophylactic effect against cancer development, as seen in the anti-proliferative effect now demonstrated both *in vitro* and *in vivo*[308]. Lastly, a case report that highlights the spontaneous regression of brain cancers in two teenagers, was associated with current medical *Cannabis* use[309].

HIV/AIDS

Cannabis has proven effective in improving the quality of lives of many individuals living with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS). Cannabinoid-based medicine is useful for the syndrome of HIV's effects – to help manage appetite loss, wasting, nausea, vomiting, pain, anxiety, stress, depression, and other concomitant symptoms associated with *both* the disease *and* the anti-retroviral regimen used to treat it. As many as one in four people living with HIV/AIDS use *Cannabis* for medical purposes in the U.S.[310].

An international group of nursing researchers determined from a longitudinal, multi-country, multi-site, randomized-control clinical trial that *Cannabis* is frequently used to manage the six common symptoms of HIV/AIDS. A 2009 study found that a significant percentage of those with HIV/AIDS find *Cannabis* to be efficacious for treating their anxiety, depression, fatigue, diarrhea, nausea, and peripheral neuropathies. Researchers noted that "those who did use marijuana rate it as effective as prescribed or over the counter medicines for the majority of common symptoms…[311]."

In addition to the debilitating symptoms of the disease itself, *Cannabis* has proven to be effective in controlling the unpleasant effects of the drugs used to treat HIV/AIDS. According to a 2007 study, people living with HIV/AIDS who use *Cannabis* to combat the side-effects of the Highly Active Antiretroviral Therapy (HAART therapy) are approximately *three times* more likely to remain on their prescribed drug therapies than those who do not use *Cannabis*[312].

In the 1970s, a series of human clinical trials established that *Cannabis* can stimulate food intake and thus, can cause weight gain in healthy volunteers – a finding confirmed by numerous subsequent studies. In a randomized trial in people living with AIDS, THC was seen to both significantly improve appetite and decrease nausea, in comparison to the effects of placebo administration. There were also trends towards both improved mood and weight gain. Unwanted effects – e.g. dry mouth, drowsiness and anxiety – were of generally mild or moderate intensity, and were proven to be of little consequence to the

user[205,313,314]. The IOM's comprehensive review in *Marijuana and Medicine* concluded, "For patients such as those with AIDS or who are undergoing chemotherapy and who suffer simultaneously from severe pain, nausea, and appetite loss, cannabinoid drugs might offer broad-spectrum relief not found in any other single medication."

To address concerns involving *Cannabis*-based medicines decreasing treatment efficacy, an FDA-approved preliminary safety trial of smoked *Cannabis*, conducted in 2003 at the University of California, San Francisco, concluded that neither synthetic THC nor inhaled *Cannabis* had any significant effect on the immune system or viral load. Moreover, the researchers noted that those study participants who used *Cannabis* gained weight[205].

In addition to the overall safety demonstrated in these trials, cannabinoids may also inhibit the spread of the HIV virus within the human body by acting directly on CD4+ T cells – T cells are critical to immune function and are a target of the HIV virus. A 2012 study found that a cannabinoid activating CB_2 receptors selectively produced a dose-specific reduction of HIV infection by up to 50%[311,315-317]. This study suggests that therapeutic use of cannabinoids might help to fight the spread of the HIV virus to uninfected T cells in the late stages of HIV-1 infection[318]. Previous research has shown that the use of cannabinoid drugs in patients with HIV is associated with an increase in CD4+ T cell number and has been shown to reduce viral load in an animal model of HIV.

Neuropathic Pain

The effectiveness of *Cannabis* and cannabinoids in managing pain has been demonstrated in more than three dozen preclinical and clinical trials, comprising more than 6,000 patient-years of data as of 2012[126]. A 2009 review noted simply: "a large number of research articles have demonstrated the efficacy of cannabinoids…[and so] cannabinoids show promise for treatment of neuropathic pain[318]."

More than one-third of people living with HIV/AIDS suffer from excruciating nerve pain in the hands or feet, frequently in response to the antiretroviral therapies that constitute first-line treatment for HIV/AIDS. This induced neuropathic pain is extremely difficult to treat and, as a result, many individuals reduce or discontinue their HIV/AIDS therapies.

A series of clinical studies of HIV/AIDS patients demonstrated that cannabinoids can significantly reduce neuropathic pain and promote weight gain, *without* compromising the immune system[319-321]. Research conducted by the University of California, San Francisco involving a randomized, placebo-controlled clinical trial of 50 people who had experienced neuropathic pain for a group average of six years, showed that smoked *Cannabis* was both well-tolerated and proved to effectively relieve chronic neuropathic pain from HIV-associated sensory neuropathies[321]. Other double-blind, placebo-controlled clinical trials with people living with HIV neuropathic pain that was not adequately controlled by other pain-relievers, including opiates, found that *Cannabis* provided significant pain relief[320]. Research also demonstrates that the use of *Cannabis* and opiates is not associated with an increase in mortality[322].

More recent randomized clinical trials conducted by the CMCR have also demonstrated that smoked *Cannabis* is effective in treating neuropathic pain[323]. Researchers found that over half of patients with

painful HIV peripheral neuropathy experienced pain reduction of more than 30% when treated with cannabinoids, a level of relief that pain researchers correlate to improved life quality. Such improvements occurred in two CMCR trials of patients with HIV peripheral neuropathies, and in a separate trial of patients with mixed neuropathic pain due to peripheral or central dysfunction of the nervous system[324-327].

Additional double-blind, placebo-controlled clinical trials indicate that *Cannabis*-based medicines may improve neuropathic pain associated with multiple sclerosis and mixed neuropathies resulting from herpes, trauma and vascular problems[126]. This research is also of particular importance to people with cancer, as many of its sufferers also experience neuropathic pain.

Finally, researchers have found that cannabinoids such as THC work *in concert* with opiate-based painkillers, to increase their combined effectiveness, particularly in cases of neuropathic pain. This evidenced synergy of *Cannabis* and opiates allowed patients to reduce their opiate dosage, minimizing the inherent risks of opiate use[328-331]. This entourage effect extends to other cannabinoids, with multiple studies finding that isolated synthetic cannabinoids such as THC (dronabinol) did not provide the same degree of efficacy as whole-plant preparations of *Cannabis*[104]. The ECS is proposed to interact with the endorphin system, both through the release of opioid peptides by cannabinoids and by the release of endocannabinoids by opioids[126,332]. Clinically, THC may enhance the pain relieving effects of opiates, effectively lowering the dose of an opiate necessary for relief[321,332]. Similarly, animal work on combined *Cannabis* and opiate administrations suggests that THC can decrease the side effects of opiates and may have a prophylactic effect on the dependence developed to opiate administration[333]. Data gathered from the U.S. in those territories that have legalized *Cannabis* for adult use, has evidenced *significantly* lower opiate-related mortality[322]. Surveys also suggest that *Cannabis* is often used to decrease the use of other drugs, most significantly opiate-based painkillers[334].

Hepatitis-C Virus

Cannabis may improve the effectiveness of drug therapy for the hepatitis C virus (HCV), a potentially deadly viral infection that affects more than 3 million Americans [335] and 130–150 million people globally. Treatment for HCV typically involves months of therapy with two powerful drugs – interferon and ribavirin – both of which have severe side effects, including extreme fatigue, nausea, muscle aches, loss of appetite, and depression. Due to the debilitating side effects of anti-HCV drug therapies, people often do not finish treatment, which worsens their symptoms and can promote irreversible harm to the liver.

Researchers from the University of California, San Francisco Medical School and the Organization to Achieve Solutions in Substance-Abuse (OASIS) found that "modest *Cannabis* use may offer symptomatic and virological benefit to some patients undergoing HCV treatment by helping them maintain adherence to the challenging medication regimen[336]." Other research has found that patients with HCV who used cannabinoids while undergoing combination ribavirin and interferon treatment were nearly *three times more likely* to complete their conventional medical treatment as compared to those participants who did not use cannabinoids.

These studies offer suggestive evidence that for patients fighting HCV, *Cannabis*-based medicine might significantly improve appetite, while offering concomitant psychological benefits such as a reduced prevalence of depression.

Chronic Pain

According to the American Academy of Pain Management, nearly 50 million Americans and more than 1.5 billion people worldwide suffer from chronic pain. Unfortunately, it is estimated that four out of every 10 people living with moderate-to-severe pain have yet to experience significant relief. After reviewing a series of trials in 1997, the U.S. Society for Neuroscience concluded that "substances similar to or derived from marijuana could benefit the more than 97 million Americans who experience some form of pain each year[267]."

Although a wide variety of prescription analgesic drugs are available for use in treating pain – from aspirin to oxycodone – *none* of these drugs can be seen as completely adequate, in light of the many, severe, and potentially deadly side-effects associated with continued opiate use.

By contrast, the safety record of *Cannabis* is remarkable, and centuries of use as an analgesic are well documented[337,338]. In their meta-analysis of the available data, the IOM acknowledged a wide historical use of *Cannabis* for pain, noting that "after nausea and vomiting, chronic pain was the condition cited most often to the IOM study team as a medicinal use for marijuana[160]." Currently, pain relief is by far the most common condition for which physicians recommend the use of cannabinoids.

Many well-designed, double-blind placebo-controlled clinical trials have demonstrated cannabinoids can reduce suffering due to neuropathic pain[175,324,339-342]. A broad review of the body of scientific research concerning the analgesic effects of *Cannabis* concluded that there is now unequivocal evidence that cannabinoids can be significantly anti-nociceptive (capable of blocking pain transmission) in known animal models of acute pain[332,343-346]." Further research shows that cannabinoids also produce an entourage effect that enhances the effectiveness of opiate painkillers. One animal study found that the pain-relieving dose of morphine was lowered with the addition of a simultaneous, small dose of THC. Codeine's efficiency was similarly enhanced[332].

Both human and animal studies have demonstrated that cannabinoids can work synergistically with opioidergic drugs in relieving pain. Research suggests that both direct and indirect interactions between opioid and cannabinoid receptors can not only enhance analgesia but also reduce the development of tolerance to opiates in mammals. These interactions hold promise for developing therapeutic strategies that could provide better pain relief, with lower overall doses of opiates (oxycodone and hydrocodone), resulting in fewer dangerous, debilitating side effects that patients reliant on opiate pain-killers alone experience[346,347].

Some of the most encouraging clinical pain data involve the treatment of intractable cancer pain and hard-to-treat neuropathic pain, a type of chronic nerve pain that resists conventional treatment. Approximately 3-4.5% of the global population and somewhere between 25% and 45% of cancer patients experience neuropathic pain. Decades of research on *Cannabis'* effectiveness in pain management include

several clinical human trials, with volumes of additional anecdotal evidence[318,348-353]. The prevailing scientific evidence suggests a significant efficacy of cannabinoids in treating neuropathic pain[126,175,318,339,354].

Multiple clinical trials have shown that a controlled-dosage whole-plant extract of *Cannabis* (nabiximols, GW Pharmaceuticals Ltd.) significantly relieves intractable cancer pain, and does so better than THC alone. A recent double blind, randomized, placebo-controlled trial of 360 cancer patients in 14 countries found that pain scores improved significantly with administration of *Cannabis* extract. Researchers report that the combination of natural cannabinoids in nabiximols "is an efficacious adjunctive treatment for cancer-related pain" for patients who do not get adequate relief from opiate painkillers such as oxycodone or hydrocodone[355,356].

Pain resulting from spinal cord injuries (SCI) may also be treatable with cannabinoid medicines. A research team in 2009 noted that "very few pharmacological studies have dealt specifically with neuropathic pain related to SCI," suggesting that "[for] refractory central pain, cannabinoids may be proposed on the basis of positive results in other central pain conditions (e.g. multiple sclerosis)." Animal model research of SCI pain has shown that cannabinoids yield more consistent positive results than conventional analgesics such as opiates, which "decrease in efficacy with repeated treatment over time". These investigations concluded that drugs targeting the body's cannabinoid receptors "hold promise for long-term use in alleviating chronic SCI pain[116]."

Researchers have also determined that neuropathic pain may be treatable via augmenting the body's natural supply of cannabinoids – the endocannabinoids. A study that inhibited two enzymes that normally break down the body's natural production of endocannabinoids found that preserving this efflux "reduces neuropathic pain through distinct receptor mechanisms of action" and that "[these compounds] present viable targets" for developing new analgesic drugs[357]. Drugs which can selectively target CB_2 cannabinoid receptors – which are almost completely absent from the central nervous system – have also demonstrated suggestive therapeutic potential for both inflammatory and neuropathic pain control[358].

Multiple Sclerosis

One survey of people living with multiple sclerosis (MS) showed that more than 40% of respondents report using *Cannabis* to relieve symptoms of the disease. Among them, nearly three quarters stated that cannabinoid medicines mitigated their muscle spasms, and more than half reported a significant alleviation of their pain. A similar survey found that 96% of Canadians living with MS believe *Cannabis* is therapeutically useful for treating the disease. Of those who admitted using cannabinoids to treat their symptoms of MS, the majority cited significant relief of chronic pain, spasticity, and depression[359]. In addition, numerous studies have reported improvements in tremor, sexual dysfunction, bowel and bladder dysfunction, vision dimness, dysfunctions of walking and balance (ataxia), memory loss, pain, and spasticity[360-367].

In fact, cannabinoids have been shown to significantly lessen MS symptoms, and slow or halt the progression of the neurodegenerative disease in mammals. Cannabinoid-based medicines have demonstrated effects on immune function that might serve to reduce the autoimmune

neuroinflammatory response which drives relapsing neurological attacks resulting in increasing disability[368-370]. Clues as to *why* may lie in research that indicates that individuals with MS show *increased* levels of endocannabinoids in their blood, indicating perhaps that the endocannabinoid system "may be dynamically modulated depending on the subtype of the disease[371]."

Pre-clinical studies of the pharmacology of *Cannabis* have identified calmative effects on those motor systems of the CNS that have the potential to positively affect tremor and spasticity. A controlled study of the efficacy of THC in an animal model of MS – experimental allergic encephalomyelitis (EAE) – demonstrated significant amelioration of these two most common MS symptoms. A review of six randomized controlled trials of *Cannabis* extracts (that combines THC and CBD) found "a trend of reduced spasticity in treated patients" and "evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms[369]." One such dosage-controlled THC-CBD whole-plant extract – the sublingual spray, nabiximols – has been shown in numerous clinical trials to ease pain, decrease spasm frequency, and improve bladder control and quality of sleep. Clinical trials of nabiximols found "a statistically significant and clinically relevant improvement in spasticity…and was well tolerated in MS patients[372]." As of June 2012, nabiximols is available by prescription in the UK, Spain, Germany, and Denmark for the symptomatic relief of spasticity, neuropathic pain, or both, in adults with MS. It has now been approved for distribution in Italy, Sweden, Austria, and the Czech Republic, with recommendations for approval in Belgium, Finland, Iceland, Ireland, Luxembourg, the Netherlands, Norway, Poland, Portugal, and Slovakia.

MS patients frequently report that cannabinoids can help alleviate bladder control issues, and a review of studies on cannabinoid receptors in the bladder notes that non-psychoactive cannabinoids are effective, and that the psychotropic effects of THC can be mitigated by delivering cannabinoids directly into the bladder[373]. While objective measures of spasticity in humans have not consistently shown benefits from cannabinoid treatment, a randomized clinical trial with 189 MS patients being treated with a *Cannabis* extract showed that 40% achieved greater than 30% improvement[374].

In addition to studying the potential role of *Cannabis* and its derivatives in the treatment of MS-related symptoms, scientists are exploring the potential of cannabinoids to inhibit neurodegeneration. A 2003 study that the National MS Society called "interesting and potentially exciting" demonstrated that cannabinoids were able to slow the disease process in mice by offering neuroprotection against EAE[375]. Only recently have scientists identified EAE as an animal model for MS, opening the door for future investigations research into MS symptom suppression.

Other Movement Disorders

Muscular spasticity is a common condition, affecting over 12 million people worldwide. It afflicts individuals who have suffered strokes, as well as those with MS, cerebral palsy, paraplegia, quadriplegia, and a variety of spinal cord injuries. Conventional medical therapy offers little relief for spasticity. Phenobarbital (a barbiturate) and diazepam (Valium, a benzodiazepine) are commonly prescribed, but they rarely provide complete relief and many patients develop a tolerance, become addicted, or complain of heavy sedation. These drugs also often cause muscle weakness, drowsiness, and a syndrome of various untoward other side effects that patients often find intolerable.

The therapeutic use of *Cannabis* for treating muscular spasticity and movement disorders has been known to Western medicine for nearly two centuries. In 1839, Dr. William B. O'Shaughnessy noted both the plant's muscle relaxant and anti-convulsant properties, writing that medical doctors had "gained an anti-convulsive remedy of the greatest value[337]." Contemporary animal and human clinical studies reveal that *Cannabis* and its constituent cannabinoids may effectively treat movement disorders affecting older patients, including tremors and spasticity, because cannabinoids have a dose-dependent anti-spasticity, analgesic, anti-tremor, and anti-ataxic effect[360,364,376-382].

The contemporary understanding of the actions of *Cannabis* was advanced by the discovery of the endogenous cannabinoid system in the human body – the ECS – which appears to be intricately involved in regulating normal physiology[141,383,384]. Central cannabinoid receptors are densely located in the basal ganglia, the area of the brain that controls body movement. Endogenous cannabinoids also appear to play a role in the manipulation of other transmitter systems within the basal ganglia – increasing transmission of certain chemicals, inhibiting the release of others, and affecting how still others are absorbed[135,385,386]. Most movement disorders are caused by a dysfunction of the biochemical loops in this part of the brain. Research suggests that an endogenous cannabinoid "tone" participates in the overall control of movement[67,387-389]. Endocannabinoids have modulating effects on the nervous system – sometimes to block neuronal excitability, while other times augmenting it. As scientists are developing a better understanding of the physiological role of endocannabinoids, it is becoming clear that these chemicals may be involved in the pathology of several neurological diseases. This means researchers are identifying an array of potential therapeutic targets within the human nervous system. They have determined that various cannabinoids found in the *Cannabis* plant modulate the synthesis, uptake, or metabolism of the endocannabinoids that underlie the progression of diseases such as Huntington's, Parkinson's, and tremors[390].

The neuroprotective qualities of *Cannabis* suggest an enormous potential for protecting the brain and central nervous system from the damaging effects of various diseases or injuries. Researchers have found that cannabinoids fight the debilitating effects of strokes, brain trauma, and spinal cord injury, as well as MS and neurodegenerative diseases. A neurodegenerative or neurological condition affects more than 52% of people over the age of 85. More than 100 research articles have been published on how cannabinoids act as neuroprotective agents, slowing the progression of a host of neurological disorders in mammals including amyotrophic lateral sclerosis, Huntington's, Alzheimer's, and Parkinson's disease[391-393].

Modern research has demonstrated some promising therapeutic effects of cannabinoids to treat Parkinson's disease and related motor neuron diseases. In one example, a female patient with Parkinsonian tremor who had failed conventional treatment claimed several hours of relief after smoking *Cannabis* on three different occasions[394]. However, when she and four other treatment-resistant patients with tremor were administered *Cannabis*, no benefit was observed on tremor in any of them in comparison to diazepam, levodopa/carbidopa or apomorphine. Two subsequent clinical trials with *Cannabis*-based medicines to treat tremor of MS, with an obviously distinct pathophysiology, produced variable benefits in some patients employing an oromucosal spray or oral extract of THC and CBD, respectively[375,395]. Data suggest that the symptom complex of Parkinsonism – including tremor,

bradykinesia, and dyskinesia – may respond to such treatment over a long time course.

The best evidence for cannabinoid efficacy in Parkinson's derives from a survey performed in the Czech Republic – after a well-publicized television news magazine program presented the story of one Parkinson disease patient who improved all his symptoms with prolonged administration of an oral *Cannabis* preparation[391]. Parkinsonian patients at the Prague Movement Disorders Centre were sent an anonymous questionnaire to assess the effects of *Cannabis* on their various symptoms. Of 630 possible respondents, 339 questionnaires (53.8%) were returned. Eighty-five respondents (25.1%) reported using fresh or dried leaves taken orally approximately ½ teaspoon (2.5 ml) with meals once a day, usually in conjunction with their customary conventional medication. Almost none had prior experience of recreational *Cannabis* usage. In marked contrast to most surveys, only one respondent smoked the *Cannabis*. As a result of this oral *Cannabis* intake, 45.9% reported mild-to-substantial reduction in overall symptoms, with 30.6% noting reduced resting tremor, 44.7% alleviation of bradykinesia, 37.7% reduced muscular rigidity, and 14.1% reduction in dyskinesia associated with L-dopa medication. Noteworthy to the report was that only 4.7% felt that *Cannabis* intake exacerbated their condition.

A limited number of studies of CBD in Parkinson's disease have also been completed in Brazil[396-398]. In the first study, six Parkinson's patients with psychosis (each non-responsive for 3 months to conventional medications) were assessed in a four-week open label study. Patients were started on 150 mg CBD capsules in corn oil, with weekly increases according to clinical response[397]. Significant improvements were noted after CBD treatment in nearly *all* scored criteria, including anxiety and depression. No change was noted in motor function, nor were any cognitive changes observed.

A second study from Brazil selected 21 patients without psychiatric or dementia diagnoses from a larger cohort of 119 consecutive Parkinson's diseases evaluations [396] and employed 300 mg CBD per day in corn oil capsules vs. placebo, in a double-blinded trial for six weeks. Capsules were administered only at night. After treatment, the CBD group showed positive results in the Parkinson's Disease Questionnaire (PDQ-39) and the Activities of Daily Living and Stigma subscores.

A third Brazilian study examined a subset of Parkinson's patients with rapid eye movement (REM) sleep behavior disorder[398]. Case studies and assessments were performed on four affected patients. Three of the patients went six weeks without episodes after taking 75 mg of CBD in corn oil capsules nightly, while the fourth required dose escalation to 300 mg a night to reduce episodes to once a week. All the patients experienced relapse to attacks of the prior frequency upon discontinuation of the CBD.

An Israeli study examined 22 patients who had received government permission to try smoked *Cannabis* for treatment-resistant Parkinsonian symptoms[399]. Participants used *Cannabis* continuously for more than two months. Six proved intolerant to *Cannabis* due to inability to inhale smoke, and side effects such as vomiting, dizziness, or psychosis. Motor scores improved after *Cannabis* in patients with or without daily response fluctuations. Specifically, improvements were noted in tremor, rigidity, bradykinesia, but only slightly on posture. Pain also diminished significantly, and 20 patients reported improvement in sleep.

The available evidence to date suggests a possible application of *Cannabis*-based medicines for

symptomatic treatment of Parkinson's disease. Both THC and CBD components may contribute, but exact dosing and/or appropriate ratios of these disparate cannabinoids are still unclear using available data[400,401]. Documentation supports a benefit to inhaled and oral preparations, with the latter seemingly preferable to patients given the requirement for chronic or life-long administration. No clear drug-drug interactions have yet been noted. Overall, the data would suggest that prolonged trials of *Cannabis*-based medicines may be necessary to assess overall benefit or lack thereof.

Arthritis

According to the Arthritis Foundation, arthritis is one of the most prevalent chronic health problems and the nation's leading cause of disability amongst Americans. A 2006 report estimated that 46 million Americans – nearly 1 in 5 adults – and 350 million people worldwide, live with chronic joint pain and arthritis. Indeed, the use of cannabinoids as a treatment for musculoskeletal pain in western medicine dates back to the 1700s[402]. Modern research confirms that *Cannabis* and related therapies can relieve the pain associated with arthritis and the other rheumatic and degenerative hip, joint, and connective tissue disorders. In their 1999 meta-analysis of the data then available, the IOM specifically noted that the anti-inflammatory properties of cannabinoids could have therapeutic application in preventing or reducing pain caused by swelling and inflammation (such as arthritis)[160].

Research has proven *Cannabis* and its constituent cannabinoids possess powerful immuno-modulatory and anti-inflammatory properties that may be useful in treating chronic inflammatory diseases directly[204,403-405]. Many patients and doctors report *Cannabis* has proven to be an effective treatment for rheumatoid arthritis, and it is one of the recognized conditions for which many U.S. states now permit medical use.

CBD has been shown to have numerous medical applications as an anti-inflammatory and neuroprotective agent, including as a treatment for rheumatoid arthritis[406,407]. Research indicates that CBD suppresses the immune response in mice and rats that is responsible for a disease state resembling arthritis, protecting them from severe damage to their joints, and markedly improving their condition [408-410]. In a randomized, double-blind, placebo-controlled trial in 58 human patients with rheumatoid arthritis, nabiximols significantly improved pain, sleep quality, and a measure of disease activity[124].

Specifically, *Cannabis* has a demonstrated ability to improve mobility and reduce morning stiffness and inflammation, and research suggests that individuals can reduce their use of potentially harmful non-steroidal anti-inflammatory drugs (NSAIDs) when using *Cannabis* as an adjunct therapy[405,411].

Alzheimer's Disease

Alzheimer's disease is a neurodegenerative condition for which *Cannabis* and cannabinoid therapies also show some promise, both for managing the symptoms and treating the underlying disease. Agitation is the most common behavioral management problem in people with Alzheimer's, affecting an estimated 75% of people with the disease. It can include symptoms ranging from physical or verbal abusive behavior to pacing and restlessness, as well as disruptive behaviors such as screaming and

repetitive requests for attention. Clinical research involving THC indicates that cannabinoids might significantly reduce the agitation common to Alzheimer's sufferers[412-414]. THC has also proven effective in combating anorexia or wasting syndrome, another common problem for people with Alzheimer's disease[415]. Alzheimer's disease is widely believed to be associated with oxidative stress, due at least in part, to the membrane action of β- amyloid peptide aggregates. Recent studies have indicated that the *Cannabis* plant's primary components – CBD and THC – provide a combination of neuroprotective, anti-oxidative and anti-apoptotic effects by inhibiting the release of the toxic β- amyloid peptide[416].

Epilepsy and Seizure Disorders

Peer-reviewed journal articles on the effects of *Cannabis* and related compounds from the plant have been largely limited to a concentrated series of preclinical animal studies, undertaken because *Cannabis* controls limit or prevent meaningful human clinical studies from being conducted in the U.S. There are *thousands* of published articles demonstrating the anti-convulsive and anti-epileptic effects of cannabinoid compounds in animals but that research is simply beyond the scope of this document, which focuses on human studies. In the absence of approved clinical research studies on *Cannabis* and epilepsy, the many anecdotal case reports of successful seizure control by individual patients must be assessed. Several documentaries have been filmed of parents using *Cannabis* extracts to treat childhood epilepsy. What follows are a number of compelling, though anecdotal, case reports of the benefit of a *Cannabis*-based therapy for seizures and convulsions[417].

Cannabis, THC, and Seizures

In the late 1940s, the effects of Δ^9-THC were investigated in a small trial of five institutionalized, epileptic children whose seizures had previously been unresponsive to phenobarbital or phenytoin. The study found that "*severe anticonvulsant resistant grand mal epilepsy* [was] *controlled*" in two children with no change noted in the remaining three[418].

Shortly before the 1976 drug convention lead to the U.S. adopting regulations that severely limited *Cannabis* research, another case report was published, documenting a 24-year-old male on two concurrent antiepileptic drugs, who was not able to control his seizures. Rather, the patient used 2-6 *Cannabis* cigarettes per day to control his symptoms[419]. Since the 1976 drug convention, there have been few relevant case studies available, and those that are available tend to document the efficacy and safety of THC-based therapy as an anticonvulsant treatment in terminal pediatric patients[378]. Another study documented four relevant cases of children, ages 12 to14, that were administered THC, causing a "noticeable reduction in the number of seizures" in these participants. More recently, *Cannabis* has been reported to produce a "marked improvement" in seizure control in a 45-year-old cerebral palsy patient, epileptic since age 18, who experienced premature birth as well as a concussion at age 8[420]. While these few anecdotal stories are quite compelling, they simply do not amply delineate *Cannabis*-based medicine for seizures.

CBD and Seizures

To date, CBD is the only phytocannabinoid other than THC with reported results for anticonvulsant effects in human subjects. The following is a review of studies on CBD used to treat seizure disorders in humans. In 1978, Mechoulam and Carlini randomized nine patients to either 200 mg/day of pure CBD or placebo[421]. During the three-month trial, two of four patients treated with CBD became seizure-free, whereas seizure frequency was unchanged in the five patients who received placebo.

A small (n=15) population of adult patients who exhibited partial seizures with secondary generalization that were uncontrolled by conventional treatment were enrolled in a double-blind, placebo-controlled, add-on study to examine the effect of CBD (≤300 mg/day) for 4.5 months[417,422,423]. Of the patients who received CBD (n = 8), four exhibited no sign of seizure, one "*improved markedly*," one "*improved somewhat*," one showed no improvement, and one withdrew from the study. The investigators concluded that CBD could be of benefit to patients with secondary generalized epilepsy for whom existing medicines were ineffective.

In a later, open-label clinical trial employing CBD (900–1200 mg/day for 10 months), "*seizure frequency was markedly reduced in the patient*" consistent with previous findings[424]. In yet another study, 12 epileptic patients were given CBD (200–300 mg/day) as an adjunct to existing treatments, but no change in seizure incidence was found[425]. The results of these studies were published in only abstract form, preventing full examination of the study details and insight into the relevance of the findings.

In 2005, a study reviewed population data of epileptic children resistant to conventional anti-epileptic medications. Subsequently, the researchers instituted treatment for *some* of these subjects using an oil-based formulation of CBD. In most of the treated children, an improvement of the crises was obtained in equal to, or higher than, 25%, wherein a clear improvement of consciousness and spasticity was observed. Specific incidence of side effects was not reported in this study; however, subjects suffered no side effects warranting discontinuation of the CBD solution.

In regards to existing research on epilepsy and *Cannabis*, most of the available human evidence suggests that *both* a reduction in incidence *and* severity of seizures, as well as physical and behavioral improvements in children and adults treated with either *Cannabis* or its preparations can be achieved.

Despite the potentially beneficial effects of *Cannabis* and its constituents in the management of epilepsy, the psychotropic effects of pure THC alone limits its widespread therapeutic use, particularly as an anticonvulsant where regular, repeated doses throughout a patient's lifetime are necessary[98,426]. However, it is notable that not only are all currently approved anticonvulsant drugs associated with some significant motoric and/or cognitive side effects, but many epilepsy patients are unable to drive motor vehicles or maintain employment because of either the side effects of conventional drugs, the symptoms of the disease, or a combination of the two[417,427].

Glaucoma

Glaucoma is an eye affliction characterized by an increase in intraocular pressure. It can lead to blindness if it is not treated effectively. Several anecdotal reports observe that *Cannabis* has the power to reduce the fluid pressure within the eye (Hepler et al., 1976; Green, 1984; Grinspoon and Bakalar, 1997). The U.S. federal government sends approximately 1 pound of *Cannabis* cigarettes to each surviving glaucoma patient from a 1970's Investigational New Drug (IND) program (there are currently two surviving patients with glaucoma)[57]. Despite documented treatment success for patients in the IND program, it was cancelled for political reasons. The surviving patients were grandfathered into the program and continue to receive *Cannabis* produced by the University of Mississippi.

Despite decades of documented anecdotal reports of *Cannabis* to treat glaucoma from this IND program, only two controlled studies evaluating the effects of THC on glaucoma patients have been approved[428,429]. In a randomized, double-blind, crossover, placebo-controlled clinical trial, Merritt et al. (1980) administered one *Cannabis* cigarette containing 2% THC to 18 adults suffering from glaucoma. *Cannabis* induced a significant reduction in intraocular pressure, but exhibited the following main adverse effects: various sensory alterations (100% of the cases), tachycardia and palpitations (44% of the cases) and postural hypotension (28%).

In the other randomized, double-blind, parallel group study against placebo, conducted 1 year later, Merritt et al. (1981) instilled eye drops containing 0.01, 0.05 or 0.1% THC in eight individuals suffering from glaucoma and hypertension (one eye received THC and the other one placebo). They then observed a significant reduction in intraocular pressure with 0.05 and 0.1% topical solutions of THC. The 0.1% topical solution of THC induced a mild hypotension, but most importantly, no psychotropic effects were observed with the three locally administered THC concentrations.

Psychiatric Disorders (Anxiety, Depression, and Related Mood Disorders)

Human studies on the effects of *Cannabis* on anxiety and depression or mood disorders include studies on THC, CBD, and whole plant material. Dosing consisted of a range between 5mg-30mg oral THC and a single clinical study looked at 0.5mg/kg THC for changes in mood and related behavior. For CBD, clinical studies examined oral doses ranging between 60mg-600mg and 1mg/kg for improvements in related mood disorders. Conversely blocking the active sites for THC with the CB_1 receptor antagonist, rimonabant is capable of increasing stress and anxiety levels at an oral dose of 70mg.

Review of the Human Clinical Studies on Psychiatric Disorders

Anxiety and Mood Disorders

The effects of *Cannabis* on anxiety and depression may depend on the ratio of certain cannabinoids, the individual user, and the context in which it is used. One of the active ingredients of *Cannabis* can cause an acute and short-lasting episode of anxiety, which often resembles panic, in naïve users. For a naïve user, a dose of oral THC that is likely to start to induce anxiety is >5mg synthetic Δ^9-THC (for a man of average weight) and a higher dose could induce both panic attacks and paranoias[94].

However, the same is not necessarily true for all cannabinoid*s*.

In a study with 10 treatment-naïve patients with generalized social anxiety disorder, 400mg oral CBD was shown to reduce anxiety compared to placebo. This anxiolytic effect was associated with significantly reduced regional cerebral blood flow (measured by uptake of 740MBq of 99mTc-ECD) in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus, while increasing cerebral blood flow (ECD uptake) in the right posterior cingulate gyrus[95]. Similarly, a study of 24 patients with social anxiety disorder found an association between CBD (600mg; n=12) and decreases in anxiety within the context of public speaking task[96].

In 1974, an interactive study between CBD and THC showed that CBD (60 mg), added to Δ^9-THC (30 mg), changed the symptoms induced by THC alone in such a way that the subjects receiving the mixture showed less anxiety and more pleasurable effects[97]. In 1982, a study confirmed a similar effect with CBD (1 mg/kg), co-administered with THC (0.5 mg/kg), and this combination also significantly reduced anxiety indices in healthy volunteers[98].

An early study on *Cannabis* use in Jamaica revealed no significant differences between a group of 30 users, and matched controls with respect to mood, thought, or behavior[99]. An international study funded by the National Institute on Drug Abuse, examined a group of 47 long-term hashish users in Greece. Differences in the number of users within defined psychopathology, as compared to controls was accounted for by "personality disorders," with more psychiatric abnormalities being observed in the moderate user group as compared to heavy users[100,101]. A few years later, another study documented that *Cannabis* users in Costa Rica believed that use helped with depression. No significant adverse effects, or development of adverse health effects resulting from *Cannabis* use were observed[44].

The effects of THC are not consistent and often may misrepresent the effects of whole *Cannabis*[102]. In a study of oral THC, healthy volunteers received two doses of THC (7.5 and 15mg by mouth) or placebo, across separate sessions, before performing tasks assessing facial emotion recognition and emotional responses to pictures of emotional scenes[102]. In this three-session, double-blind, placebo-controlled study, THC significantly impaired recognition of facial fear and anger, marginally impairing recognition of sadness and happiness. The subjective responses to THC were not consistently positive – of the 25 study participants, 15 indicated a desire to take the 7.5mg dose again, whereas only 11 out of 25 did so at the higher 15 mg dose. Just over half of the participants identified THC as "marijuana-like" (7.5mg: 56%; 15mg: 52%). This study parallels many other findings on this subject – the paradox between dampened amygdalar reactivity and increased physiological indicators of emotional response remains a mystery to be resolved. The authors concluded that this property could potentially increase the appeal of *Cannabis* to certain users. As *Cannabis* use can lead to reduced sensitivity to anxiety-provoking emotional signals in some people, this may facilitate certain social interactions, especially amongst individuals with social inhibition or related disorders.

It has been well demonstrated that 'blocking' or interfering with CB_1 receptor signaling can increase anxiety. One study documented that the CB_1 receptor antagonist/inverse agonist, rimonabant, increases anxiety induced by public speaking in healthy humans. The anxiogenic effects occurred selectively during anticipatory and performance speech, without interfering with the pre-stress phase, meaning that the

drug effects occurred selectively in response to an aversive situation[103].

Inhaled *Cannabis* and mucosal sprays – with precise amounts of key cannabinoid ingredients – do not induce the same side effects as pure THC controls[104]. Research suggests that a *Cannabis* "overdose" (i.e., anxiety, panic attack, etc.) can be treated (or prevented prophylactically) with foodstuffs such as pine nuts, lemons, basil and/or orange juice, as these foodstuffs share many relevant, pharmacologically active compounds[104].

Similar to the literature on the effects on *Cannabis* on anxiety, the effects of *Cannabis* on mood disorders are contradictory. For example, a group of authors published case reports suggesting *Cannabis* can cause an acute depressive reaction in those with underlying depression. However, their later case reports suggest *Cannabis* use can *improve* symptoms of bipolar disorders [31,101,105]. Cross sectional studies suggest that depression is associated with *Cannabis* use, and that *Cannabis* consumption is related to an increased risk of depression later in life[13,106]. Likewise for anxiety, it has been noted that "Frequent cannabis users consistently have a high prevalence of anxiety disorders and patients with anxiety disorders have relatively high rates of *Cannabis* use[94]." It is unknown whether *Cannabis* use leads to a greater incidence of depression and anxiety later in life.

In one survey, *Cannabis* use and depression were not associated once medical use was taken into account[107]. In some cases, an illness (and not the use of *Cannabis*) may be causative factor for depression. Though there is a modest increase of risk amongst problematic users of developing depression or an anxiety disorder later in life, a recent meta-analysis found that that small, but statistically significant association between *Cannabis* and anxiety hinged on the inclusion of a single study[108]. While *Cannabis* may provide some benefit to anxiety or depressive/mood disorders in some individuals, the true relationship between *Cannabis* use and anxiety and depressive disorders later in life remains unsubstantiated by current research. Similar to anxiety, differential effects of *Cannabis* on depression may be due to differences in cannabinoid composition. Indeed, CBD has been shown to produce anti-depressant like effects similar to imipramine[109,110].

Suicide and Suicidal Ideation

Recent epidemiological work found no relation between the number of medical *Cannabis* users and completed suicides[111]. In fact, U.S. states that legalized the use of medical *Cannabis* were shown to have lower rates of suicide among men between the ages of 20 and 39, when compared to states that did not legalize medical *Cannabis* use[112].

Research among non-medical *Cannabis* using populations has received considerably more attention. Unfortunately, while some studies have shown associations between *Cannabis* use and heightened suicide ideation and attempts, a number of studies have either failed to control for confounds or, when they have, reported no association between *Cannabis* use and suicide[113-118] .

Post-Traumatic Stress Disorder

There has been a recent emergence of empirical studies on the effects of *Cannabis* for symptoms of PTSD, borne primarily out of the observation that individuals with PTSD report using *Cannabis* to cope with PTSD symptoms; specifically, hyperarousal, negative affect, and sleep disturbances[119-121]. Indeed, empirical work has consistently demonstrated that the endocannabinoid system plays a significant role in the etiology of PTSD, with greater availability of cannabinoid type 1 receptors documented among those with PTSD than in trauma-exposed or healthy controls[122,123].

Unfortunately, there have been no randomized controlled trials (RCTs) of *Cannabis* for the treatment of PTSD. However, the use of *Cannabis* and oral THC has been implicated as a potential mechanism for the mitigation of many PTSD symptoms by way of its effects on the endocannabinoid system[430,431]. Consistent with this research, there has been one small RCT of nabilone that showed promise for reducing nightmares associated with PTSD. This retrospective study identified a 75% reduction in PTSD symptoms following *Cannabis* use among combat veterans with PTSD. In an unpublished pilot study of 29 Israeli combat veterans, reductions in PTSD symptoms followed the administration of smoked *Cannabis*, with effects seen up to one year post-treatment[432,433].

Research on Cannabis and Gastrointestinal Disorders

Crohn's disease (CD) is an inflammatory bowel disease (IBD) that has no cure; treatment targets include reducing inflammation and secondary symptoms[434]. Between 16 percent and 50 percent of patients use *Cannabis* to relieve symptoms of IBD and patients using *Cannabis* for 6 months or longer are five times more likely to have had surgery for their IBD[202,435-437]. Only one placebo-controlled study of the effects of *Cannabis* in patients with CD has been conducted[436]. This study found that there was no difference between placebo and smoked *Cannabis* on CD remission, defined as a CD Activity Index (CDAI) of less than 100, and that *Cannabis* was superior to placebo in promoting clinical response (a decrease in CDAI score greater than 100), reducing steroid use, and improving sleep and appetite[436].

Many researchers have concluded that pharmacological modulation of the endogenous cannabinoid system provides new treatment options for a number of gastrointestinal diseases, including nausea and vomiting, gastric ulcers, IBD, CD, secretory diarrhea, paralytic ileus and gastroesophageal reflux disease[438-440] .

List of Medical and Scientific Organizations that have Issued Letter of Support for Medical Cannabis

Numerous professional, medical, and scientific organizations, have issued their support for medical cannabis programs through public statements and testimony. A few examples are listed below:

> *The National Cancer Institute, one of 11 federal agencies under the National Institutes of Health, changed its website to include Cannabis as a Complementary Alternative Medicine, with possible benefits for people living with cancer. http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq - section/all*

> *"Based on much evidence, from patients and doctors alike, on the superior effectiveness and safety of whole cannabis (marijuana) compared to other medicines for many patients — suffering from the nausea associated with chemotherapy, the wasting syndrome of AIDS, and the symptoms of other illnesses … we hereby petition*

the Executive Branch and the Congress to facilitate and expedite the research necessary to determine whether this substance should be licensed for medical use by seriously ill persons." - American Academy of Family Physicians

The American Medical Association "urges that marijuana's status as a federal Schedule I substance be reviewed with the goal of facilitating the conduct of clinical research and development of cannabinoid-based medicines."

The American College of Physicians "urges an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule."

The American Public Health Association "adopted a resolution [...] which urged federal and state drugs laws to exclude Marijuana as a narcotic drug," and "conclude[d] that cannabis was wrongfully placed in Schedule I of Controlled Substances, depriving patients of its therapeutic potential."

"Marijuana should be available for appropriate medicinal purposes, when such use is in accordance with state law, and that physicians who recommend and prescribe marijuana for medicinal purposes in states where such use is legal, should not be censured, harassed, prosecuted or otherwise penalized by the federal government."- American Preventive Medical Association

"The Texas Medical Association supports (1) the physician's right to discuss with his/her patients any and all possible treatment options related to the patients' health and clinical care, including the use of marijuana, without the threat to the physician or patient of regulatory, disciplinary, or criminal sanctions; and (2) further well-controlled studies of the use of marijuana with seriously ill patients who may benefit from such alternative treatment."

The Rhode Island Medical Society has stated that "[T]here is sufficient evidence for us to support any physician-patient relationship that believes the use of marijuana will be beneficial to the patient."

A 2004 testimony from the New York County Medical Society stated, "The definitive review of scientific studies ... found medical benefits related to pain relief, control of nausea and vomiting, and appetite stimulation. ... While there are a variety of ways of supplying marijuana for medical use, serious consideration should be given to the 1997 recommendation ... that the FDA reclassify marijuana from Schedule I and provide a consistent, safe supply."

"The American Medical Student Association strongly urges the United States Government ... to meet the treatment needs of currently ill Americans by restoring the Compassionate (Investigational New Drug) program for medical marijuana, and ... reschedule marijuana to Schedule II of the Controlled Substances Act, and ... end the medical prohibition against marijuana."

"The National Nurses Society on Addictions urges the federal government to remove marijuana from the Schedule I category immediately, and make it available for physicians to prescribe. NNSA urges the American Nurses' Association and other health care professional organizations to support patient access to this medicine."- The National Nurses Society on Addictions

"The American Cancer Society supports the need for more scientific research on cannabinoids for cancer patients, and recognizes the need for better and more effective therapies that can overcome the often debilitating side effects of cancer and its treatment. The Society also believes that the classification of marijuana as a Schedule I controlled substance by the US Drug Enforcement Administration imposes numerous conditions on researchers and deters scientific study of cannabinoids. Federal officials should examine options consistent with federal law for enabling more scientific study on marijuana.

> *"The Society supports the rights of people with MS to work with their MS health care providers to access marijuana for medical purposes in accordance with legal regulations in those states where such use has been approved. In addition, the Society supports advancing research to better understand the benefits and potential risks of marijuana and its derivatives as a treatment for MS."- National Multiple Sclerosis Society*

> *"The Epilepsy Foundation supports the rights of patients and families living with seizures and epilepsy to access physician directed care, including medical marijuana. Nothing should stand in the way of patients gaining access to potentially life-saving treatment. If a patient and their healthcare professionals feel that the potential benefits of medical marijuana for uncontrolled epilepsy outweigh the risks, then families need to have that legal option now — not in five years or ten years. For people living with severe uncontrolled epilepsy, time is not on their side. This is a very important, difficult, and personal decision that should be made by a patient and family working with their healthcare team."*

> *"(T)he Leukemia & Lymphoma Society supports legislation to remove criminal and civil sanctions for the doctor-advised, medical use of marijuana by patients with serious physical medical conditions."*

The above list represents a small portion of organizations that have offered their support for access to medical *Cannabis.*

FACTORS 4 & 5: ITS HISTORY AND CURRENT PATTERN OF ABUSE & THE SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

To assess drug abuse patterns and trends, data from different sources have been analyzed such as National Household Survey on Drug Abuse (NHSDA), Monitoring the Future (MTF), Drug Abuse Warning Network (DAWN), and Treatment Episode Data Set (TEDS) have been analyzed.

According to a recent United Nations (UN) report, the prevalence of *Cannabis* use in the Netherlands, where *Cannabis* has been de facto legal for the last 40 years, is lower than in many other European countries, the U.S. and Canada[441]. Four jurisdictions in the U.S. have legalized *Cannabis*, those are Colorado, Alaska, Washington state and Washington, DC.

It is estimated that somewhere between 3.3-4% of the world's population (age 16-64 years) used *Cannabis* once in the last year according to the UN Office on Drugs and Crime.

Use and Abuse

The reviews of marijuana rescheduling petitions by government agencies do not distinguish between use and abuse according to professional standards, such as those in use by the medical and scientific community. There are existing standards such as the *ICD-10 codes*, which distinguish between use, abuse, and dependence[442]. Widespread use of *Cannabis* is not an indication of its abuse potential, and widespread use of marijuana without dependency supports the argument that marijuana is safe for use under medical supervision.

Since marijuana, heroin and other drugs are often referred to as "drugs of abuse", many consider each use of these drugs "abuse". That a clear differentiation between the two terms if often lacking is suggested by

Wish (1990), who noted in an editorial of *the Journal of the American Medical Association* on drug screenings in the workplace that a discussion on the difference between drug use and drug abuse was often regarded as "anachronistic and unpatriotic[443]."

However, the term "substance abuse" is clearly defined and should be differed from simple and unproblematic use, which is the rule and not the exception with most drugs, even in adolescents. Scientists usually differentiate between use, and forms of problematic use. The most frequent terms for problematic or pathological use are abuse, misuse, harmful use and dependency (e.g. Gorman and Derzon 2002, Swift et al. 2001)[444,445]. Definitions for these terms vary so that samples determined using different definitions overlap. Swift et al. (2001) compared dependency according to the DSM-IV (Diagnostic Manual of Diseases) to the concept of dependency in the ICD-10 (The International Classification of Diseases, 10th Revision) in a sample of 10,641 representative Australian adults:

> *"The prevalence of DSM-IV (1.5%) and ICD-10 (1.7%) cannabis dependence was similar. DSM-IV and ICD-10 dependence criteria comprised uni-dimensional syndromes. The most common symptoms among dependent and non-dependent users were difficulties with controlling use and withdrawal, although there were marked differences in symptom prevalence. Dependent users reported a median of four symptoms. There was good to excellent diagnostic concordance (kappas = 0.7-0.9) between systems for dependence but not for abuse/harmful use (Y = 0.4). These findings provide some support for the validity of cannabis dependence."*

According to the newer DSM-IV definition *Cannabis* abuse and dependency will be observed more often than according to the criteria of the earlier DSM-III-R:

> *"We assessed a clinical sample of 102 adolescents using CIDI- SAM. Prevalence of either an abuse or dependence diagnosis was lower with DSM-IV than DSM-III-R except for cannabis and alcohol, and concordance rates were better for dependence than for abuse. For most substances, rates of DSM-IV withdrawal were lower than in DSM-III-R, but rates of DSM- IV physiological dependence remained high. Changes in DSM- IV criteria appear to have impacted diagnoses in these adolescents, particularly for the substances they use most--i.e. alcohol, tobacco, and cannabis[446]."*

Clinical criteria for substance abuse according to DSM-IV are:

> *A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one or more of the following occurring within a twelve-month period.*
>
> *(1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g. repeated absences or poor work performance related to substance use, substance related absences, suspension, or expulsions from school; neglect of children or household).*
>
> *(2) Recurrent substance use in situations in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use).*

(3) Recurrent substance related legal problems (e.g. arrest for substance related disorder conduct).

(4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by effects of substance (e.g. arguments with spouse about consequences of intoxication, physical fights).

B. Symptoms have never met the criteria for substance dependence for this class of substance.

When talking about the gateway theory, the Institute of Medicine (Joy et al. 1999) pointed out that it is necessary to differentiate between use and dependency or abuse to draw the right conclusions from given data:

> *"Many of the data on which the gateway theory is based do not measure dependence; instead, they measure use -even once- only use. Thus, they show only that marijuana users are more likely to use other illicit drugs (even if only once) than are people who never use marijuana, not that they become dependent or even frequent users. The authors of these studies are careful to point out that their data should not be used as evidence of an inexorable causal progression; rather they note that identifying stage-based user groups makes it possible to identify the specific risk factors that predict movement from one stage of drug use to the next -the real issue in the gateway discussion[171]."*

Modern epidemiological studies have shown that many people who use *Cannabis* do not differ from other people, that they do not abuse the drug but use it. A survey of 15,000 British children aged 14 and 15 found that young people with high self-esteem are more likely to take illicit drugs than those whose self-confidence is low (Observer of 11 February 2001). The results contradict the concept that drug use is most prevalent among anxious or insecure youth looking for an escape from poor conditions or a way to feel better about themselves. Heather Ashton, a professor of pharmacology at Newcastle University, said that the results of the survey did not surprise her: "Students all report they take drugs for pleasure and that it has nothing to do with anxiety or stress. Years ago young people who take drugs were seen as psychotic or low risk-takers. Now that is not the case."

A report published by the Institute of Medicine provides an equally clear assessment of contemporary scientific standards for defining drug use, abuse, and dependency. The report "Pathways of Addiction, Opportunities in Drug Abuse Research" was published in 1996. According to its introduction:

> *"The report employs the standard three-stage conceptualization of drug-taking behavior that applies to all psychoactive drugs, whether licit of illicit. Each stage -- use, abuse, dependence -- is marked by higher levels of use and increasing serious consequences. Thus, when the report refers to the "use" of drugs, the term is usually employed in a narrow sense to distinguish it from intensified patterns of use. Conversely, the term "abuse" is used to refer to any harmful use, irrespective of whether the behavior constitutes a "disorder" in the DSM-IV diagnostic nomenclature. . . . It bears emphasizing that adverse consequences can be associated with patterns of drug use that do not amount to abuse or dependence in a clinical sense, although the focus of this report and the committee's recommendations is on the more intensified patterns of use (i.e, abuse and dependence) since they cause the*

> *majority of serious consequences." (Committee on Opportunities in Drug Abuse Research, 1996)*

The findings above clarify marijuana's abuse potential relative to other drugs; the use of more dangerous drugs is not a significant risk for most individuals whose consumption of marijuana can be described as use rather than abuse or dependence. These findings affirm that medical users of marijuana are not at risk to use of other illicit drugs due to their regular use of *Cannabis*.

The College on the Problems on Drug Dependence recognizes that marijuana is not a harmless drug, but they note a basis for distinguishing marijuana from drugs such as cocaine and heroin. They also note that serious questions have been raised as to whether marijuana is sufficiently dangerous to justify criminal sanctions, and are critical of DEA's irrational scheduling decisions with respect to marijuana:

> *"Despite these significant adverse effects, questions have been raised by various investigative commissions about whether the social costs associated with the prohibition of marijuana are warranted by its actual harm to individuals and society, and especially whether imprisonment for mere possession unaccompanied by other crimes -- the law in some states -- is appropriate. It can be argued that placing marijuana in the same category as heroin and cocaine also sends a counterproductive message because it erases distinctions among drugs with very different degrees of hazard." (College on the Problems of Drug Dependence Annual Meeting, 1997).*

Gorman (2002) uses data from several prospective longitudinal studies (N= 3206) to examine the association between three psychological constructs on the use, misuse, and abuse of marijuana – providing an example of research and analytical strategies that incorporate the distinctions discussed above[444]. Many drug users not only do not move on to more dangerous drugs, many of them also stop using drugs on their own as they age.

> *"[This research] examined patterns of illicit drug use, abuse, and remission over a 25-year period and recent treatment use. . . .[utilizing] Retrospectively obtained year-to-year measures from the 1996-1997 survey included use and remission of sedatives, stimulants, marijuana, cocaine, and opiates, as well as substance abuse and psychiatric treatment use. . . . Most drug abusers who had started using drugs by their early 20s appeared to gradually achieve remission. Spontaneous remission was the rule rather than the exception. Nonetheless, considerable unmet needs existed for those who had continued use into middle age[447,448]."*

Abuse of Cannabis

Several studies demonstrate that abuse rates for *Cannabis* are lower than rates for other common drugs. *Cannabis* use is usually not problematic use and *Cannabis* users usually have no social problems,

which can be attributed to *Cannabis*. The abuse potential of *Cannabis* is insufficient to justify prohibition of medical use.

Several studies demonstrate that abuse rates for *Cannabis* are lower than rates for other common drugs. *Cannabis* use is usually not problematic use and *Cannabis* users usually have no social problems, which can be attributed to *Cannabis*. The abuse potential of *Cannabis* is insufficient to justify prohibition of medical use.

In a sample of 10,641 Australians aged 18 years and older, 2.2% of adults were diagnosed with DSM-IV *Cannabis* use disorder, comprising *Cannabis* dependence (1.5%) and *Cannabis* abuse (0.7%)[445]. In this sample, 21% of *Cannabis* users met criteria for *Cannabis* dependence and 10.7% for abuse. Thus, there were a considerable number of *Cannabis* users in this sample with substance use disorders without being dependent. In this sample, *Cannabis* dependence was twice as likely to occur as *Cannabis* abuse.

Most *Cannabis* use is not problematic even for adolescents. In a survey of 2641 UK school students aged 15-16 years, 201 students reported having used *Cannabis* 40 times or more. They were examined using cluster analysis and also compared to other students.

> *"Three clusters of heavy cannabis users emerged. The smallest was largely distinguished by antisocial behaviour. Another cluster were clearly unhappy, with little support from parents and friends, high levels of depressed mood and low levels of self-esteem. The largest cluster were 'ordinary' and had little to distinguish them apart from a belief that their environment was stable and predictable and that society's rules should be obeyed. Although clear relationships emerged between heavy cannabis use and heavy use of other substances, the 'ordinary' cluster of heavy cannabis users were less likely than the others to have used other illicit drugs. It is therefore concluded that teenage heavy cannabis users have varied motivations and contexts for their usage. They should not be seen as a homogeneous group and many do not appear to use other illicit drugs[449]."*

Often *Cannabis* users are treated as a homogeneous group, usually when attempting to analyze a correlation with the use of other drugs, with mental illnesses (depression, schizophrenia), or to find predictors for a certain development (e.g. Griffin et al. 2002, Degenhardt et al. 2001). Degenhardt et al. (2001) analyzed relationships between alcohol, *Cannabis* and tobacco and indicators of mental health problems[450]. Alcohol users had lower rates of affective and anxiety disorders than non-users of alcohol, while those meeting criteria for alcohol dependence had the highest rates. Tobacco and *Cannabis* use were both associated with increased rates of all mental health problems examined.

However, after controlling for demographics, neuroticism and other drug use, *Cannabis* was not associated with anxiety or affective disorders. Alcohol dependence and tobacco use remained associated with both of these indicators of mental health. All three types of drug use were associated with higher rates of other substance use problems, with *Cannabis* having the strongest association. It should be noted that researchers differentiated alcohol use and alcohol dependence and found very different results, while no such differentiation was made for *Cannabis*.

It is well established that most users of legal drugs, notably alcohol, tobacco and caffeine, control their use and are not generally considered to be abusing the drug. It appears from cluster analyses that this is also the case with *Cannabis* and that studies, which do not use cluster analyses and do not distinguish use from problematic use will overlook relevant information.

The associations that are found with *Cannabis* have also been found with legal drugs. Degenhardt and Hall (2001) examined the comorbidity between tobacco use, substance-use disorders and mental health problems among Australian adults aged 18 years and over[451]. DSM- IV diagnoses of substance use, anxiety, and affective disorders were derived using the Composite International Diagnostic Interview (CIDI). Other measures included a screener for psychosis and measures of psychological distress and disability. Researchers found that current tobacco use was strongly associated with abuse/dependence upon alcohol, *Cannabis*, and other substances, and with higher rates of anxiety and affective disorders. Current smokers were more likely to screen positively for psychosis and reported greater psychological distress and disability than non-smokers and persons who had never smoked. These higher rates of other problems were not explained by differences in demographic characteristics, neuroticism scores, or by use of other drugs. The authors concluded:

> ***"Current tobacco use is associated with a range of other substance-use and mental health problems. These are likely to reduce the success of attempts to quit smoking. The presence of these other problems needs to be considered when considering smoking-cessation treatment, and further research may provide information on more effective treatment strategies for persons with co-existing substance-use and mental health problems."***

Another article by Degenhardt et al. found that psychosis in a sample of 6,722 Australian adults were associated with the regular use of tobacco, alcohol, *Cannabis* and opiates[450].

> *"Ninety-nine persons (1.4%) screened positively for psychosis. Regular tobacco, alcohol and cannabis use were much more common among persons screening positively, as were alcohol, cannabis and other drug use disorders. Among alcohol and cannabis users, psychosis 'cases' were much more likely to be dependent. Ordinal logistic regressions revealed that regular tobacco use, cannabis and alcohol dependence, and opiate abuse were predictors of psychosis scores[450]."*

For marijuana, even simple associations between an undifferentiated group of users and commonly believed attributes, for example that *Cannabis* users are not ambitious in sports or at work, cannot generally be established. The French Monitoring Centre for Drugs and Drug Addictions (OFDT) conducted a national school survey on the relationship between sporting activities and alcohol, cigarette and *Cannabis* use among adolescents[452]. Respondents were asked confidentially by self-administered

questionnaire (pen and paper) about their use of licit and illicit drugs and life-style (including sporting activities outside school: hours per week, registration in a club, type of sport).

The U-shaped curve between the intensity of physical activities and licit and illicit drug use appeared not to be systematic. It depended mainly on the product and the level of use. It only remained significant for boys and heavy smoking once gender and age effect were taken into account. The results stress the need to control for age and gender when the survey participants are teenagers. The relationship between drug use and sporting activity also depends on the type of sport[452].

One criteria of substance abuse deals with the "failure to fulfill major role obligations at work, school, or home." There are several studies dealing with the effects of *Cannabis* use on school and work performance, with conflicting results.

McDaniel (1988) analyzed the relationship between pre-employment drug use and on-the-job performance and found only a small positive correlation[453]. Blank and Fenton (1989) found a positive association between positive pre-employment testing for marijuana and later dismissals[454]. On the other side, Parish (1989) did not find any relation between pre- employment drug testing result and performance at work[455]. Normand et al. (1990) did not find any association between drug test results and subsequent change in employment[456]. Zwerling et al. (1990) noted a positive association between *Cannabis* use and change of occupation, absenteeism and discipline related problems at work[457]. One year later they reassessed the same cohort and found that there was no longer an association between *Cannabis* use and absence from work, while discipline-related problems had decreased[458]. These studies relied on results from pre-employment drug testing and suggest that only a minor sub-set of *Cannabis* users suffers from problems at work.

A study by Braun et al. (2000) demonstrated that the *Cannabis* effect is modulated by cultural aspects[459]. This was a nearly population based study on the prospective interrelationship of smoking, alcohol intake, marijuana use, and educational and occupational attainment of black and white young adults. Researchers used data from the U.S. CARDIA study (Coronary Artery Risk Development in Young Adults), which involved 5,115 persons 18-30 years of age during the 1985-86 period, who were reevaluated in 1987/88, 1990/91, 1992/93 and 1995. At the start of the study, 28.0% stated that they had used *Cannabis* in the past month. In the following 10 years, *Cannabis* use was negatively associated with completion of college. However, this negative association was only found in the younger sub-set aged 18-24 years at the start of the study, while in the older sub-set there was only a negative association between tobacco use and college completion. Associations of substance use with occupational measures were dependent on skin color.

> ***"In Whites, marijuana use was associated with less prestigious occupations and lower family income, while smoking was unrelated and moderate daily drinking was positively associated. In Blacks, marijuana use was generally unrelated to occupational measures, while smoking and daily alcohol consumption were negatively associated{Braun:2000jd}."***

Another criteria of substance abuse deals with "recurrent substance use in situation in which it is physically hazardous (e.g. driving an automobile or operating a machine when impaired by substance use)." Culpability studies provide the best data on the problems *Cannabis* can cause in the context of driving. This method studies crashes *post hoc* based upon information (usually from coroners and/or police data) about the causative factors of a crash and blood analyzes on drugs. Examination of these causative factors permits the researchers to apportion a score for each crash-involved driver to determine culpability for the crash. Although there are some differences between studies, these scores classify each driver as "culpable", or "not culpable" for the crash. The cases are then divided into groups according to the results of the blood analysis. Those drivers who had no detectable drugs in blood constitute the control group. A recent analyzes summarizes:

> *"To date (September 1999), seven studies using culpability analysis have been reported, involving a total of 7,934 drivers. Alcohol was detected as the only drug in 1,785 drivers and together with cannabis in 390 drivers. Cannabis was detected in 684 drivers and in 294 of these was the only drug detected. (...) Using the culpability analysis method the dominant role of alcohol in motor vehicle accidents is clearly demonstrated, confirming the results with the case-control method. The results to date of crash culpability studies have failed to demonstrate that drivers with cannabinoids in blood are significantly more likely than drug-free drivers to be culpable in road crashes[460]".*

If urine instead of blood is analyzed, predominantly drivers with regular *Cannabis* use will be found and not those actually impaired since *Cannabis* use can be detected for some weeks in the urine of heavy users. In a U.S. study with 414 injured drivers, 32 of the urine samples were positive for at least one potentially impairing drug[461]. Marijuana was detected most frequently (17%), surpassing alcohol (14%). Compared with drug- and alcohol-free drivers, the odds of crash responsibility were higher in drivers testing positive for alcohol alone (odds radio [OR] = 3.2) and in drivers testing positive for alcohol in combination with other drugs (OR = 3.5). Marijuana alone was not associated with crash responsibility (OR = 1.1). In a multivariate analysis, controlling for age, gender, seat belt use, and other confounding variables, only alcohol predicted crash responsibility. Researchers concluded:

"Alcohol remains the dominant drug associated with injury- producing traffic crashes. Marijuana is often detected, but in the absence of alcohol, it is not associated with crash responsibility[461]."

The first controlled, population based study on accidents on *Cannabis* users compared to non- users was conducted by Braun et al. (1998) in the U.S. Researchers and compared 4,462 individuals with different *Cannabis* use status (never, former, current use) with regard to frequency of injuries within three years[462]. Participants were randomly selected from 64,862 patients of a health maintenance program aged 15 to 49 years. All injuries independently of cause and severity were included. A total of 2,524 accident victims were treated outpatient, 22 were treated inpatient and 3 were fatalities. There was no association between *Cannabis* use and injuries.

The abuse potential of a certain substance can also be determined from the variation in the intensity of use over the course of several years. A high variability in intensity indicates a weak potential for

dependency and abuse. Von Sydow et al. (2001) determined incidence and patterns of the course of *Cannabis* use and disorders as well as cohort effects in a community sample of adolescents and young adults (n=2,446) aged 14-24 years at the outset of the study[463]. Patterns of *Cannabis* use, abuse and dependence (DSM-IV) were assessed using the Composite International Diagnostic Interview (M-CIDI). They reported the following results:

(1) Cumulative lifetime incidence for *Cannabis* use (at second follow-up): 47%; 5.5% for *Cannabis* abuse, 2.2% for dependence. (2) Men used and abused *Cannabis* more often than women. (3) The majority of the older participants (18-24 years at baseline) had reduced their *Cannabis* use at follow-up, while younger participants (14-17 years at baseline) more often had increased their use and developed abuse or dependence. (4) The younger birth cohort (born 1977-1981) tended to start earlier with substance (ab)use compared to the older birth cohort (1970-1977). (5) *Cannabis* use was associated with increasing rates of concomitant use of other licit and illicit drugs. The authors concluded:

> **"Cannabis use is widespread in our sample, but the probability of developing cannabis abuse or dependence is relatively low (8%). The natural course of cannabis use is quite variable: about half of all cannabis users stopped their use spontaneously in their twenties, others report occasional or more frequent use of cannabis[464]."**

Felder and Glass (2001) explain that the abuse potential of *Cannabis* is not sufficient to preclude its medical use[465]. Their assessment of the relative abuse potential of *Cannabis* suggests that it does not have the high potential for abuse required for Schedule I or II status.

Much of the political and public objection to the use of THC or *Cannabis* as a therapy centers around its abuse potential and the belief by some that it serves as a "gateway" drug leading users to "harder" drugs of abuse. Many therapeutic drugs have abuse potential, yet this does not invalidate their role in current therapies. While there is some preliminary evidence for cannabinoids activating the reward pathways in the brain, most investigators have failed to find addictive or reinforcing effects of cannabinoids in animal models[466]. Unlike cocaine or heroin, cannabinoid agonists produce conditioned place aversion even at low doses and anxiogenic effects[467-469].

Furthermore, some species or varieties of animals will not self-administer cannabinoids and a lack of cross-sensitization between cocaine or amphetamines and cannabinoids has also been demonstrated[465,470-475]

A considerable number of *Cannabis* users suffer from problems that meet the criteria for abuse. However, the large majority of *Cannabis* users do not experience any relevant problems related to their use. When compared to legal drugs, abuse problems with *Cannabis* are generally less severe. The abuse of *Cannabis* does not preclude its medical use. Relative to other scheduled drugs *Cannabis* does not have a high potential for abuse.

Cannabis and Dronabinol

There is growing evidence that there is no relevant difference in subjective effects between (Schedule III) dronabinol and *Cannabis*. Thus, it can be expected that the abuse liability is similar for both agents.

There is growing evidence that there is no relevant difference in subjective effects between (Schedule III) dronabinol and *Cannabis*. Thus, it can be expected that the abuse liability is similar for both agents.

In 1999, the Drug Enforcement Administration (DEA) reclassified dronabinol (Marinol) from a "Schedule II" drug to the less restrictive "Schedule III" category according to the Controlled Substances Act. This essentially means that instead of being classified with drugs like morphine, dronabinol is now classified with more widely used drugs like codeine. According to the Associated Press of July 3, 1999, Barry McCaffrey, director of the White House Office of National Drug Control Policy, said the capsule form of dronabinol is the "safe and proper way" to make components of marijuana available to the public and "this action will make Marinol, which is scientifically proven to be safe and effective for medical use, more widely available"

There are not many direct comparisons of the subjective and medicinal effects of *Cannabis* and dronabinol (THC, Dronabinol). Recent experimental research has shown that the subjective effects of *Cannabis* and THC are very similar[476]. The authors write:

> *"There has been controversy about whether the subjective, behavioral or therapeutic effects of whole plant marijuana differ from the effects of its primary active ingredient, Delta(9)-tetrahydrocannabinol (THC). However, few studies have directly compared the effects of marijuana and THC using matched doses administered either by the smoked or the oral form.*
>
> *Two studies were conducted to compare the subjective effects of pure THC to whole-plant marijuana containing an equivalent amount of THC in normal healthy volunteers. In one study the drugs were administered orally and in the other they were administered by smoking.*
>
> *In each study, marijuana users (oral study: n=12, smoking study: n=13) participated in a double-blind, crossover design with five experimental conditions: a low and a high dose of THC-only, a low and a high dose of whole-plant marijuana, and placebo. In the oral study, the drugs were administered in brownies, in the smoking study the drugs were smoked. Dependent measures included the Addiction Research Center Inventory, the Profile of Mood States, visual analog items, vital signs, and plasma levels of THC and 11-nor-9-carboxy-THC.*
>
> *In both the oral study and the smoking study, THC-only and whole plant marijuana produced similar subjective effects, with only minor differences.*
>
> *These results support the idea that the psychoactive effects of marijuana in healthy volunteers are due primarily to THC[476]".*

Since the abuse potential of a drug is mainly attributed to its subjective effects it can be assumed that the abuse potential of THC and *Cannabis* are quite similar.

Clinical research has also demonstrated similar properties of THC and *Cannabis* with regard to therapeutic effects. This is shown in the data from marijuana research programs on the anti-emetic effects of marijuana in 6 states (Musty & Rossi 2001, see above), where patients who smoked marijuana experienced 70-100% relief from nausea and vomiting, and those who used the THC capsule experienced 76-88% relief[261]. In the study by Abrams et al. (2002) that investigated the interaction of smoked *Cannabis* and dronabinol (THC) with HIV medication, very similar effects were observed with regard to weight gain. The participants had been divided into three groups, with one set smoking *Cannabis* (3.95% THC), another taking oral dronabinol capsules (3x2.5 mg daily), and a third taking oral placebo capsules. Researchers found that those using dronabinol (THC) or *Cannabis* experienced significant increases in caloric intake and gained an average of 3.5 kg (marijuana group) and 3.2 kg. (THC group) compared to 1.3 kg in the placebo group. There was no significant difference between *Cannabis* and THC with regard to side effects and benefits.

Leo Hollister stated in a recent review on the medical use of *Cannabis*:

> ***"Marinol or dronabinol, is available for treating nausea and vomiting associated with cancer chemotherapy and as an adjunct to weight loss in patients with wasting syndrome associated with AIDS. Although such approval currently applies only to orally administered THC, for practical purposes smoked marijuana should also be expected to be equally effective. Promising leads, also often fragile, suggest possible uses for treating chronic pain syndromes, neurological disease with spasticity and other causes of weight loss. These indications require more study."***

The American public notes that the difference between *Cannabis* and dronabinol with regard to classification is hypocritical and political. Journalist Cynthia Cotts commented the reclassification of Marinol from Schedule II to Schedule III in the Nation on September 20, 1999:

> *"For more than half a century, the U.S. government has maintained a hard line on marijuana, denying that the plant has any medical value at all. But in the period since 1996, during which voters in several states have approved the medical use of marijuana and the Institute of Medicine has hailed the therapeutic effects of THC (one of the cannabinoids found in the natural plant), the Feds have scrambled to revise their position. Now, the drug warriors' line goes something like this: Who needs pot, an illegal substance that burns up your lungs, when you can take Marinol (dronabinol), a little white pill that contains synthetic THC? The government threw its weight behind Marinol this past July, when the Drug Enforcement Administration moved the drug into Schedule III, lifting its dangerous stigma and making it easier for doctors to prescribe. While drug czar Barry McCaffrey insisted the move was based on "pure science," a review of the players involved suggests that the rise of Marinol is more the result of politics and profiteering[477]".*

Cannabis as Gateway Drug

Recent research suggests that recreationally used *Cannabis* does not act as a gateway drug to harder drugs such as alcohol, cocaine and heroine. The same will apply to users of medicinal *Cannabis*.

Several research studies addressed the question whether *Cannabis* leads to the use of harder drugs such as alcohol, cocaine and heroin. The Institute of Medicine study characterized marijuana's role as a "gateway drug" as follows:

> *"Patterns in progression of drug use from adolescence to adulthood are strikingly regular. Because it is the most widely used illicit drug, marijuana is predictably the first illicit drug most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. In fact, most drug users begin with alcohol and nicotine before marijuana—usually before they are of legal age.*
>
> *In the sense that marijuana use typically precedes rather than follows initiation of other illicit drug use, it is indeed a "gateway" drug. But because underage smoking and alcohol use typically precede marijuana use, marijuana is not the most common, and is rarely the first, "gateway" to illicit drug use. There is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs. An important caution is that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes. It does not follow from those data that if marijuana were available by prescription for medical use, the pattern of drug use would remain the same as seen in illicit use[171]."*

A more recent study based on national survey data also does not support the hypothesis that increases in marijuana use lead to increased use of more dangerous drugs among the general public. In the *American Journal of Public Health*, Andrew Golub and Bruce Johnson of the National Development and Research Institute in New York wrote that young people who smoked marijuana in the generations before and after the baby boomers do not appear to be likely to move on to harder drugs[478]. The researchers said that these findings suggest that the gateway phenomenon reflects norms prevailing among youths at a specific place and time.

"The recent increase in youthful marijuana use has been offset by lower rates of progression to hard drug use among youths born in the 1970s. Dire predictions of future hard drug abuse by youths who came of age in the 1990s may be greatly overstated."

Research also suggests that the "gateway theory" does not describe the behavior of serious drug users:

> *"The serious drug users were substantially different from high school samples in their progression of drug use. The serious drug users were less likely to follow the typical sequence identified in previous studies (alcohol, then marijuana, followed by other illicit drugs). They were more likely to have used marijuana before using alcohol, and more likely to have used other illicit drugs before using marijuana. We also found that atypical sequencing was associated with earlier initiation of the use of illicit drugs other than marijuana and greater lifetime drug involvement. These findings suggest that for a large number of serious drug users, marijuana does not play the role of a 'gateway drug'. We conclude that prevention efforts which focus on alcohol and marijuana may be of limited effectiveness for youth who are at risk for serious drug abuse[479]."*

Side Effects of the Legal Situation

The illegal status of *Cannabis* under most jurisdictions causes negative consequences for many with regard to their career, personal and professional relationships, suspension of driving privilege, and health.

In a book chapter on side effects of the medical use of *Cannabis*, Grotenhermen states:

> *"Natural cannabis products are illegal in most countries. For the most part, no legal distinction is made between recreational and medical use. If single cannabinoids (dronabinol, nabilone) that may be legally prescribed in some countries are not available, too expensive, or ineffective, therapeutic use of cannabis may provoke various repercussions for the patient who employs it. These include: criminal prosecution or fear thereof, paying a high price for an illegal drug, exposure to possible contamination, use of an unknown concentration of THC with possible variability in dosing, limited forms of administration, and even fear of discussion with the patient's family doctor. The illegality of cannabis presents various obstacles to clinical research[168]."*

At this time, U.S. law on the federal level and in most states treats the medicinal and recreational uses of marijuana and related acquisition alike. Thus, the legal situation of medical *Cannabis* users is subject to the same negative implications of law enforcement and penalization.

FACTOR 6: WHAT, IF ANY, RISK THERE IS TO THE PUBLIC HEALTH

This section discusses research on public health priorities regarding prenatal and adolescent exposure, *Cannabis* use and the workplace, and emergency room visits. Additionally, a summary of the toxicological data from Factor 1 is discussed here.

Overview Prenatal and Adolescent Exposure to Cannabis

Cannabis and cannabinoids are recommended and prescribed to treat neurological disorders, and are not associated with causing significant neurological problems or having a toxic effect on development in controlled research studies[60,62,66,101,126,417,480]. A CDPHE Retail Marijuana Public Health Advisory Committee review of *Cannabis* and pregnancy states that negative effects associated with prenatal exposure to *Cannabis* are "mixed" and "limited" because research does not show significant harms to IQ, brain structure and function (Kathryn Wells, MD. Pediatric Marijuana Exposure DDHS Training August 11, 2015)[481]. Despite evidence that THC can be present in breast milk, there is no evidence to support the claim that THC has profound and long-lasting consequences for the brain. A recent study confirms the safety profile of *Cannabis*, "maternal marijuana use does not increase the risk of adverse obstetrical outcomes or fetal anomalies[482]."

Exposure to *Cannabis* and related products may produce acute side effects such as anxiety, paranoia, or temporally inhibiting memory. However there is no supporting evidence that indicates that these side effects predict the development of conditions (such as anxiety condition or other mental health issue) later in adult life. There is also no significant impact on IQ or scholastic performance regardless of the amount of *Cannabis* use or exposure, once other factors are controlled for (tobacco, alcohol, access to medical care, brain injuries (stroke, concussion), etc).

Children (Development Pre- and Post-Natal)

The science demonstrates that cannabinoid receptor activation (i.e. CB_1 and CB_2 receptors) is a natural and important component for proper development[483]. Mammals, including humans, produce endocannabinoids, which are THC-like compounds. These THC-like compounds include Anandamide and 2-AG. Anandamide and 2-AG activate the same receptors as THC, and are found in bovine and human breast milk[484]. Adding THC to the mix of endocannabinoids in breast milk may lead to changes in development but scientists have no significant evidence that the differences in rats and mice translate into long-term negative changes in human development because[151]. For example, rats exposed to THC during adolescents are protected from developing opiate dependence, which suggest *Cannabis* use could prevent developing dependence or addiction to other drugs [333].

The claims of negative developmental effects from THC exposure remain unsubstantiated but the blocking of cannabinoid receptor activation during early development is considered to have "catastrophic" effects. Studies by Ester Fride and colleagues have demonstrated the importance of having an endocannabinoid system that is actively functioning[66,101,483,485-487]. For example, one of the studies by Fride et al. showed that the administration of SR141716A, a drug which prevents CB_1 receptor activation by THC and anandamide, will kill 50% of baby mice within 2 days, due to a disruption of feeding behavior[488]. In another experiment from the same study, THC was able to reverse the rate of death and disruption in feeding behavior induced by SR141716A.

Studies in mice and rats have shown that prenatal or postnatal exposure to *Cannabis* or cannabinoids may lead to subtle changes in breast milk and development. However, many of these animal studies do not have much, if any human data to corroborate them. Drugs abuse studies are often difficult to interpret, as most subjects use multiple drugs and socioeconomic status seems to play the biggest role–money, health care, and your parents level of education can have a bigger impact on healthy development than *Cannabis*[489].

Many studies have looked at the effect of *Cannabis* use during pregnancy and the results suggest that there are not clear consequences. A review article published by Dr. Ethan Russo walks the reader through the human studies on pregnancy, here are some of the examples from his article[490]:

> *"A variety of studies have demonstrated transient effects of cannabis on endocrine hormone levels, but no consistent effects seem to occur in chronic settings[490]."*

> *"Studies are hampered by the obvious fact that laboratory animals are not human in their responses. Estrous cycles and behaviors in animals are not always analogous to menstrual cycles and other physiological effects in women[490]."*

"In a study of 171 women, 25% of pregnancies ended spontaneously within 6 weeks of the last menses. Cannabis exposure seemed to have no observable effect in these cases[491]."

"In 1987, the Ottawa group compared effects of cannabis, tobacco, alcohol and caffeine during gestation. Whereas tobacco negatively affected neonatal birth weight and head circumference, and alcohol was associated with lower birth weight and length, no effects on any growth parameters were ascribable to maternal cannabis usage[492]."

"In a subsequent study, examination of 8350 birth records revealed that 417 mothers (5%) claimed cannabis-only usage in pregnancy, but no association was noted with prematurity or congenital anomalies. The authors suggested that previously ascribed links to cannabis were likely confounded by concomitant alcohol and tobacco abuse[493]."

"A group in Boston noted a decrease in birth weight of 79 g in infants born to 331 of 1226 surveyed mothers with positive using drug screen for cannabis (p =0.04), but no changes in gestation, head circumference or congenital abnormalities were noted[494]."

"The largest study of the issue to date evaluated 12,424 pregnancies. Although low birth weight, shortened gestation and malformations seemed to be associated with maternal cannabis usage, when logistic regression analysis was employed to control for other demographic and exposure factors, this association fell out of statistical significance[495]."

"Dreher has extensively examined prenatal cannabis usage in Jamaica wherein the population observations were not compounded by concomitant alcohol, tobacco, or polydrug abuse[496,497]. This study is unique in that regard, no less due to the heavy intake of cannabis ("ganja"), often daily, in this cohort of Rastafarian women. No differences were seen between groups of cannabis-using and non-cannabis-using mothers in the weight, length, gestational age or Apgar scores of their infants. "Deleterious effects on progeny of cannabis smokers were not apparent; in fact, developmental precocity was observed in some measures in infants born to women who smoked ganja daily[496]."

Researchers have administered THC and other cannabinoids to children; cannabinoids may have a role in pediatric medicine as young children do not appear to get "high" from cannabinoids such as THC[498]. Below is a discussion of two of the clinical trials on cannabinoids and children.

> ***"The gradual postnatal increase of anandamide and its CB_1 receptors is accompanied by a gradual maturing response to the psychoactive potential of D9-tetrahydrocannabinol and anandamide in postnatal mice between birth and weaning[499]."***

This observation has important implications for cannabinoid therapy in children, since psychoactive side effects may be expected to be minor when treated with cannabinoids at a young age. Indeed, very high doses of D8-tetrahydrocannabinol (approximately 0.64 mg/kg/treatment) were given to children between the ages 3 and 13 years who were undergoing chemotherapy for the treatment of various hematologic cancers, over long periods of time (up to 114 treatments, based on 4 treatments/24h during the days of chemotherapy). The anti-emetic effects were impressive, whereas the side effects were

minimal[500].

In a report entitled, *On the application of cannabis in paediatrics and epileptology*, eight children (ages 3-14 years) with a variety of severe neurological diseases were treated with D9-tetrahydrocannabinol (0.04-0.12 mg/kg/day) [378]. Significant improvements in behavioral parameters including reduced spasticity, improved dystonia, increased interest in the surroundings and antiepileptic activity were reported without notable adverse effects[378].

It is not clear, how, in the first study, the anti-emetic effects were achieved (presumably via the area postrema) and in the second, positive neurological benefit was derived in the absence of adverse psychological effects.

Is it possible that a differential CB_1 receptor distribution appears during development, or that differential maturation of brain pathways is responsible for the clinical success? Clearly, further animal experiments and clinical investigations of cannabinoid treatment in the developing organism are warranted but *Cannabis* exposure prenatally or during adolescence appears to not have a significant effect on development.

Emergency Room Admissions

Data on both drug treatment and emergency room admissions also distinguish the abuse potential of marijuana from that of other drugs, and establishes its relative abuse potential as lower than Schedule I drugs such as heroin and Schedule II drugs such as cocaine[462,501,502].

According to the Treatment Episodes Data Set, nearly 54% of all marijuana treatment admissions are referred to by the criminal justice system, compared to much smaller percentages for heroin and cocaine. The abuse potential of the more dangerous drugs is so severe that addicts seek treatment on their own or through persuasion from the people they have contact with. Furthermore, marijuana treatment admissions are much more likely to receive ambulatory drug treatment such as outpatient care than opiate or cocaine admissions, another indication that marijuana has a lower potential for abuse.

The relative abuse potential of drugs can also be evaluated by comparing the likelihood of the respective user populations to be admitted to emergency rooms as a result of their drug use. According to the 1998 National Household Survey, there were 18.7 million annual marijuana users, 3.8 million annual cocaine users, and 253,000 annual heroin users. According to 1998 data from the Drug Abuse Warning Network (DAWN), based on reports from participating hospital emergency rooms, there were 76,870 emergency room mentions for marijuana, 172,014 mentions of cocaine, and 77,645 mentions of heroin/morphine. Incorporating both sets of data indicates that rates of emergency room mentions per 100,000 users is 411 for marijuana, 4,514 for cocaine, and 30,690 for heroin. The table demonstrates that users of marijuana in the U.S. are much less likely to be admitted to emergency rooms than those of cocaine and heroin.

Thus, national survey data provide additional evidence that marijuana does not have a high potential for abuse relative to other controlled substances.

Cannabis Drug Testing and Impairment in Driving and at the Workplace

Access programs for medical and adult use of *Cannabis* raises questions around the issue of workplace safety and driving. Evidence from traffic and fatality databases suggests that cases of DUI related traffic fatalities and drug overdoses are either not significantly increasing or significantly decreasing in States with *Cannabis* access program[322,503]. This trend is occurring at a time when toxicology testing for the presence of any *Cannabis* metabolite is becoming more routine[322,504].

There are concerns regarding the possibly of impaired workers on any medicine or legal drug, presents a dilemma for employers. While drug testing can determine if a worker has consumed *Cannabis* or any drug, there is no way to determine from drug testing the date & time when the worker took the drug and there is a very poor correlation between impairment and plasma levels of drugs. Plasma, blood, or urine levels of benzodiazepine, cocaine, opiates, anti-depressants and almost every other drug have a very poor correlation with intoxication or impairment[505-512]. Meaning that sobriety testing by a drug test (at work or the roadside) has little meaning in terms of public safety. In fact, using the data on DUI's in the U.S. in a meaningful way is problematic, in terms of predicting public health harms because DUI's for a drug are issued for the presence of the drug in a blood or similar test indicating past use within no specific time frame (i.e., sometime during the last month); these DUI's related to drug testing are not issued based on traffic violations, traffic faults, or any required evidence of actual impairment or intoxication. For example, some U.S. states have a zero tolerance policy, meaning the drug does not have to be quantified or within a limit of quantification, to bureaucratically qualify as intoxication. Furthermore, toxicology tests like those conducted after a fatal roadside accident typically do not report the levels the drugs, toxicology reports from traffic fatalities do no list the concentration or amount of drugs that were detected in a tissue or fluid, thus the reports are not useful for determining impairment or intoxication[513].

The metabolites of *Cannabis* products can remain in the body for up to three or even four weeks or months depending on the type of test (hair, urine, blood, etc.), a worker who is not impaired and can safely handle job responsibilities may be at risk of losing his job due to laws not based on any scientific or clinical evidence.

Drug testing, whether based on blood or urine sampling, can detect cannabinoid metabolites for up to 3-4 weeks following consumption. New or occasional users may show impairment at lower concentrations quicker than chronic users, but the minimum amount of time before the drug is no longer detectable in urine or bloodstream is generally at least 3-4 days after use. This indicates workers who fail a drug test for *Cannabis* metabolites may have no impairment unless they consumed *Cannabis* shortly before or during work. Both the National Highway Traffic Safety Administration and the National Institute on Drug Abuse have stated that marijuana impairment testing via blood sampling is unreliable[514-517]. Drug tests generally produce false-positive results in 5%-10% of cases and false negatives in 10-15% of cases[518].

The solution to this common challenge of drug testing according to the National Workrights Institute is to implement impairment testing, which has been shown to be more reliable than using a blood, urine, or hair test for an unscientifically determined, detectable amount of a drug[519]. The National Workrights

Institute has stated that "the available information indicates that impairment testing is not just a better answer on paper, but in practice as well. Employers who have used impairment testing consistently found that it reduced accidents and was accepted by employees. Moreover, these employers consistently found that it was superior to urine testing in achieving both of these objectives[520,521]."

There are advantages for impairment testing over blood & urine testing for both employers and employees[522-524]. Impairment testing addresses employer concerns about human safety and protection of property. When employers promote these goals among all employees, it has the potential to reduce unreported accidents. Employees who use medical marijuana will be able to reveal it. In addition, focusing on impairment fulfills the goals of disability discrimination statutes: to protect applicants and employees with a disability who can perform successfully with reasonable accommodations by the employer. According to studies completed by the Workrights Institute: 100% of employers who used impairment testing considered their experience successful. And 82% of employers found that impairment testing improved safety[521].

FACTOR 7: ITS PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY

Dependence Liability

Basic research on rewarding, tolerance, and withdrawal.

In recent years, scientists were able to show that animals do self-administer THC under certain conditions. Basic animal research also shows that *Cannabis* produces tolerance and withdrawal. This research helps explain abuse of *Cannabis* and dependency in humans. However, basic research cannot predict how pronounced these effects will be in humans and whether they are stronger or less strong compared to other drugs such as caffeine, nicotine and heroin.

Tanda et al. (2000) demonstrated for the first time that animals self-administer THC. They write in their abstract:

> ***"Many attempts to obtain reliable self-administration behavior by laboratory animals with delta-9-tetrahydrocannabinol (THC), the psychoactive ingredient in marijuana, have been unsuccessful. Because self-administration behavior has been demonstrated in laboratory animals for almost all other psychoactive drugs abused by humans, as well as for nicotine, the psychoactive ingredient in tobacco, these studies would seem to indicate that marijuana has less potential for abuse. Here we show persistent intravenous self-administration***

> ***behavior by monkeys for doses of THC lower than doses used in previous studies, but comparable to doses in marijuana smoke inhaled by humans[525]."***

In this study Tanda and colleagues used a low but clinically relevant dose of THC administered intravenously in a clear solution. This solution rapidly distributed THC to the brain. Previous attempts to show self-administration, using much higher doses of THC held in a suspension, failed. One reason for this may be that, although higher doses were used, the suspension resulted in less brain penetration. In this study, the monkeys had previously been trained to self-administer cocaine by pressing a lever 10 times. When saline was substituted for cocaine, self-administration stopped. When THC replaced the saline, the monkeys quickly started to press the lever again. The monkeys gave themselves about 30 injections during an hour-long session, which equates roughly with the dose received by a person smoking a marijuana joint.

The team went on to confirm that giving the monkeys a second drug that directly blocks cannabinoid receptors in the brain could prevent self-administration. Dr. Goldberg's team concludes from its observations that THC "has as much potential for abuse as other drugs of abuse, such as cocaine and heroin."

However, Martin Jarvis, professor of health psychology at University College London (UK) said in an interview to the British Medical Journal this would probably overstate the case. He said that misuse is "a judgment best made by looking at patterns of actual human use." He continued: "We shouldn't assume that unreasonable behavior in society follows from the observation of brain reward behavior in animals alone[526]."

Ian Stolerman, professor of behavioral pharmacology at the Institute of Psychiatry in London, agreed with Jarvis and states during the interview: "This is an important study because for the first time it provides a method for studying directly the intake of THC by a laboratory animal and thus models a key behavioral feature of addictive states generally. It will lead to studies of how and where THC works in the brain to generate drug abuse. It does show that THC shares properties with other drugs of abuse, but whether it is really as potentially abusive as cocaine and heroin is not so clear[526]."

Several studies in recent years have demonstrated that there is an interaction between the endogenous cannabinoid system and several other transmitter and modulator systems in the brain, among them the opioid system.

Lichtmann et al. (2001) have shown that there seems to be a reciprocal relationship between the cannabinoid and opioid system relative to dependency[527]. THC was able to block some of the withdrawal symptoms in morphine dependent mice, and morphine was able to reduce some of the withdrawal symptoms in THC dependent mice. The mu-opioid receptor seems to be involved in THC dependence. These findings are consistent with the results of a study by Yamaguchi et al. (2001)[528]. Their study in mice suggests that in morphine dependence, upregulation of cannabinoid CB_1 receptors occurs. Thus, CB_1 receptor agonists may have potential as therapeutic drugs for opiate withdrawal symptoms. Successful treatment of opiate withdrawal symptoms has been described by physicians of the 19th century and in contemporary case reports.

Valverde et al. (2001) support the concept of an interaction between the cannabinoid and the opiate systems. They found several effects of THC on the opiate system in mice including facilitation of the antinociceptive and antidepressant-like responses elicited by the endogenous enkephalins and increased release of Met-enkephalin-like material in the nucleus accumbens. However, there was no modification of the rewarding responses produced by morphine from the acute or chronic administration of THC.

> *"Recent studies have suggested that cannabinoids might initiate the consumption of other highly addictive substances, such as opiates. In this work, we show that acute administration of Delta9-tetrahydrocannabinol in mice facilitates the antinociceptive and antidepressant-like responses elicited by the endogenous enkephalins protected from their degradation by RB 101, a complete inhibitor of enkephalin catabolism. This emphasizes the existence of a physiological interaction between endogenous opioid and cannabinoid systems. Accordingly, Delta9-tetrahydrocannabinol increased the release of Met-enkephalin-like material in the nucleus accumbens of awake and freely moving rats measured by microdialysis. In addition, this cannabinoid agonist displaced the in vivo [3H] diprenorphine binding to opioid receptors in total mouse brain. The repetitive pretreatment during 3 weeks of Delta9- tetrahydrocannabinol in mice treated chronically with morphine significantly reduces the naloxone-induced withdrawal syndrome.*
>
> *However, this repetitive administration of Delta9-tetrahydrocannabinol did not modify or even decrease the rewarding responses produced by morphine in the place preference paradigm. Taken together, these behavioral and biochemical results demonstrate the existence of a direct link between endogenous opioid and cannabinoid systems. However, chronic use of high doses of cannabinoids does not seem to potentiate the psychic dependence to opioids[529]."*

The neurotransmitter dopamine seems to play a major role in rewarding by drugs and physical activities, such as sex and sports. It has been suggested that the use of *Cannabis*, like that of caffeine, tobacco and other drugs, is associated with increased mesolimbic dopamine activity[530]."However, evidence for such an effect is inconsistent[531]". Stanley-Cary et al. (2002) investigated whether or not the cannabinoid agonist CP 55,940, which binds to the CB_1 receptor, mimicked the effects of amphetamine, a drug which increases dopamine release, on prepulse inhibition (PPI) of the acoustic startle reflex[531]. They write:

> *"The first experiment measured the PPI of 16 male Wistar rats injected (i.p.) with different doses of CP 55,940 in a Latin- square design. A second experiment replicated the effects of the first experiment in a between-subjects design, and also examined the effects of using a 5% alcohol solution as a solvent for cannabinoid agonists, in comparison to the more inert detergent, Tween 80. In both experiments, CP 55,940 in Tween 80 significantly reduced basal activity, increased startle onset latencies and increased PPI, effects opposite to those of amphetamine. These results suggest that the net behavioral effects of cannabinoids are opposite to those of amphetamine. In addition, it was found that 1 ml/kg of a 5% alcohol solution has significant behavioral effects on its own, and reverses the effects of CP 55,940 on PPI[531]."*

Effects of *Cannabis* use on dopamine may be complex and are not fully understood today. Studies showed that activation of dopamine receptors with a dopamine (D2-like receptor) ligand in the striatum (a region that controls planning and execution of motor behaviors) led to a strong stimulation of anandamide (an endocannabinoid) outflow[532]. The researchers concluded that the physiological role of anandamide may be "...to counter dopamine stimulation of motor activity. (...) Thus, our findings may have implications for neuropsychiatric disorders such as schizophrenia, Tourette's syndrome and Parkinson's disease and may point to novel therapeutic approaches for these conditions[532]."

In another study of this group, elevated endocannabinoid levels were found in the cerebrospinal fluid of people with schizophrenia. One explanation for the higher levels in schizophrenics is that the brain is attempting to compensate for a hyperactive dopamine system[533]. The author suggests that this could be the brain's response to try and bring this dopamine activity down but in some situations, the brain cannot keep the amount of anandamide high enough to lower dopamine levels[533].

In summary, animal studies show that THC and other ligands to the CB_1 receptor are rewarding, that they are self-administered by animals under certain conditions, and that CB_1 receptor ligands exert complex interactions with the opiate and the dopamine system. However, determining the relevance and implications of these findings to humans requires clinical studies

Dependency Compared to other Drugs

Compared to other widely used drugs (alcohol, tobacco, opiates) a smaller percentage of *Cannabis* users become dependent. Dependency is also less severe compared to many other legal and illegal drugs. The relatively low dependence liability of *Cannabis* is widely recognized.

Withdrawal from THC has been described in animal research and humans. For example, people who smoke marijuana daily become more aggressive when they quit. Dr. Elena Kouri and colleagues at Harvard University write in the *Journal of Psychopharmacology* that they had shown objectively that when people stop smoking marijuana, there is a clear withdrawal syndrome[534].

The withdrawal symptoms are relatively mild. In a review of the published literature regarding *Cannabis* withdrawal symptoms in humans, Smith (2002) stated:

> *"It is suggested that the studies conducted to date do not provide a strong evidence base for the drawing of any conclusions as to the existence of a cannabis withdrawal syndrome in human users, or as to the cause of symptoms reported by those abstaining from the drug. On the basis of current research, cannabis cannot be said to provide as clear a withdrawal pattern as other drugs of abuse, such as opiates. However, cannabis also highlights the need for a further defining of withdrawal, in particular the position that rebound effects occupy in this phenomenon. It is concluded that more controlled research might uncover a diagnosable withdrawal syndrome in human users and that there may be a precedent for the introduction of a cannabis withdrawal syndrome before the exact root of it is known[535]."*

Tolerance and rebound phenomena in humans have been described for *Cannabis*. These are other indications of dependency caused by *Cannabis*:

> *"Tolerance develops to the receptor-mediated effects of THC with continued usage. However, there are distinctions in their degree with different effects. Discontinuation of chronic THC use may cause rebound phenomena (transient increase in intraocular pressure, loss of appetite, etc.). Some chronic users report withdrawal symptoms after abrupt cessation. This withdrawal syndrome is characterized by irritability, agitation, sleep disorder, hyperhidrosis and loss of appetite. It is generally mild. Cannabis dependency is less determined by physical than by psychological factors. Dependency and abuse potential of therapeutically employed Δ9-THC is low[168]."*

Dependency rates are reported to be lower than with many other drugs. In a German study of 1,458 current or previous *Cannabis* users, ordered by the German Federal Health Ministry, 2- 10% of those using exclusively *Cannabis* were classified as substance dependent[536]. If those who also used other illegal drugs were included, 8% of *Cannabis* users were regarded as dependent, including 1% of the "occasional users," 7% of the "individual users," 10% of the "recreational users," and 28% of the "permanent users." Duration of consumption had no influence on the likelihood of the subject to quit use, an indication that the risk of dependency was independent of duration of use, and that users generally had no problems quitting.

Similar percentages were reported by Hall et al. (1999):

> *"A variety of estimates have been derived from U.S. studies in the late 1970s and early 1980s, which defined cannabis use and dependence in a variety of ways. These studies suggested that between 10 and 20 per cent of those who have ever used cannabis, and between 33 and 50 per cent of those who have had a history of daily cannabis use, showed symptoms of cannabis dependence (see Hall, Solowij & Lemon, 1994). A more recent and better estimate of the risk of meeting DSM- R.III criteria for cannabis dependence was obtained from data collected in the National Comorbitity Study (Anthony, Warner & Kessler, 1994). This indicated that 9 per cent of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32 per cent of tobacco users, 23 per cent of opiate users and 15 per cent of alcohol users[537]."*

In the recent past, several studies have attempted to compare the health risks of the most common legal and illegal drugs. Two studies received special attention: a report by order of the French Health Ministry, the so-called "Roques-Report", and a study prepared for the World Health Organization[537,538] . Major attention was paid to concerns over dependency/addiction potentially having a causative role associated with these drugs.

Both reports concluded that heavy *Cannabis* consumption causes less harm than heavy use of the most common other legal and illegal drugs. Special attention was paid to the question of dependency and abuse. Hall et al. (1999) concluded that all drugs under investigation can cause dependency[537]. The

main health risks to exclusive users of *Cannabis* would be limited to daily users who consume the drug over a period of several years. These risks included the risk of a dependency syndrome, development of a chronic bronchitis, and involvement in motor vehicle accidents if the user drives under acute influence of the drug. The latter could also affect occasional users. With regard to dependency Hall et al. (1999) conclude (as quoted above):

> *"A variety of estimates have been derived from U.S. studies in the late 1970s and early 1980s, which defined cannabis use and dependence in a variety of ways. These studies suggested that between 10 and 20 per cent of those who have ever used cannabis, and between 33 and 50 per cent of those who have had a history of daily cannabis use, showed symptoms of cannabis dependence (see Hall, Solowij & Lemon, 1994). A more recent and better estimate of the risk of meeting DSM- R.III criteria for cannabis dependence was obtained from data collected in the National Comorbidity Study (Anthony, Warner & Kessler, 1994). This indicated that 9 per cent of lifetime cannabis users met DSM-R-III criteria for dependence at some time in their life, compared to 32 per cent of tobacco users, 23 per cent of opiate users and 15 per cent of alcohol users[537]."*

Eminent addictions specialist Jack Henningfeld was asked to rate the addictive qualities of popular drugs and produced the following ratings according to five general indicators of abuse potential:

- Tolerance: How much of the substance is needed to satisfy increasing cravings for it, and the level of stable need that is eventually reached.
- Dependence: How difficult it is for the user to quit, the relapse rate, the percentage of people who eventually become dependent, the rating users give their own need for the substance and the degree to which the substance will be used in the face of evidence that it causes harm.
- Intoxication: Though not usually counted as a measure of addiction in itself, the level of intoxication is associated with addiction and increases the personal and social damage a substance may do[539].

This assessment agrees with those cited above in that marijuana ranks low on all indicators of additive potential compared to other commonly used drugs. Adolescents are more susceptible to marijuana dependence and to problems related to *Cannabis* abuse than adults.

"Adolescents are dependent at a lower frequency and quantity of use than adults: the differences diverge as level of use increases. Twice as many adolescents as adults who used marijuana near-daily or daily within the last year were identified as being dependent (35% versus 18%). Frequency and quantity of use each retained a unique effect on dependence, but frequency appeared to be more important than quantity in predicting last year dependence[540]." However, recent evidence has not produced supporting evidence long-term effects related to this finding in other, larger populations[11].

This higher dependence liability of adolescents is sometimes used as an argument against the medical use of *Cannabis*. However, this argument is not used with other medicines, such as the opiates. The IOM report states that permitting the medical use of *Cannabis* would not increase non-medical uses. The

report also addresses the suggestion by opponents of medical use that approving marijuana as a medicine "sends the wrong message." The authors say there is "no convincing data to support this concern," and they note that "this question is beyond the issues normally considered for medical uses of drugs[171]."

Kandel et al. (1997) analyzed dependency rates in a sample of about 88,000 individuals[541]. They found that nicotine was the most addictive drug. Analyses were based on three aggregated waves (1991, 1992 and 1993) of the nationally representative samples of the general population, at or above 12 years of age, interviewed in the National Household Surveys on Drug Abuse (n = 87915).

> *"The five major findings are that: (1) nicotine is the most addictive of the four drugs we examined; (2) among female last year users of alcohol and marijuana, adolescents are significantly more at risk for dependence than any other age group of women; (3) conditional prevalences of last year dependence on alcohol, marijuana and cocaine are higher among adolescent females than adolescent males but significantly different only for cocaine; (4) among adults, the rates of dependence are higher among males than among females for alcohol and marijuana, but lower for nicotine; and (5) among last year users, whites are more likely than any other ethnic group to be dependent on nicotine and blacks to be dependent on cocaine[541]."*

If selected samples of individuals are investigated, it is necessary to avoid any generalization of the results. Crowley et al. (1998) investigated a sample of young *Cannabis* users (age: 13- 19 years) with serious *Cannabis*-use disorders and problems and noted[542]:

"The prevalence of cannabis use is rising among adolescents, many of whom perceive little risk from cannabis. However, clinicians who treat adolescent substance users hear frequent reports of serious cannabis-use disorders and problems. (...) The data indicate that for adolescents with conduct problems cannabis use is not benign, and that the drug potently reinforces cannabis-taking, producing both dependence and withdrawal. However, findings from this severely affected clinical population should not be generalized broadly to all other adolescents[542]."

In conclusion, *Cannabis* can cause dependency but withdrawal is milder than withdrawal from several other legal and illegal drugs, and dependency is less frequent than with most other common legal and illegal drugs.

FACTOR 8: WHETHER THE SUBSTANCE IS AN IMMEDIATE PRECURSOR OF A SUBSTANCE ALREADY CONTROLLED

While Cannabis is not an immediate pre-cursor to a scheduled drug, purified-CBD can be converted into THC.

IV. FINDINGS AND RECOMMENDATIONS

We support the removal of *Cannabis* from Schedule I and the placement into a category, which recognizes its inherent safety and medical utility.

To reside in Schedules II-IV and be approved for diagnosing, mitigating, treating, or curing a specific medical condition, a substance or botanical must proceed through a rigors FDA process proving safety and efficacy. Different forms of *Cannabis* have been through rigorous clinical testing including whole plant *Cannabis,* hash oil extracts dissolved in ethanol, and purified extracts.

To be approved a medicine the FDA requires the following five criteria to be addressed; Based on the information from this eight factor analysis, below are the five criteria the FDA requires to be satisfied to demonstrate that Marijuana or *Cannabis* is medicine:

(1) THE DRUG'S CHEMISTRY IS KNOWN AND REPRODUCIBLE.

The chemistry of *Cannabis* is known and reproducible. *Cannabis* monographs have been published by the AHP setting guidance for standards of identity, analysis, quality control, administration, and dosing. The AHP monographs are based on FDA and USP guidelines for botanical medicines. Additionally, standardized *Cannabis* products are available from the NIDA-funded University of Mississippi marijuana farm for the FDA's IND program, a program that has provided standardized *Cannabis* cigarettes to the same participants, every month for decades. Furthermore, the Research Triangle Institute (A NIDA funded, DEA compliant organization) has also released a quality control manual for *Cannabis,* entitled *The Analytical Chemistry of Cannabis – Quality Assessment, Assurance, and Regulation of Medicinal Marijuana and Cannabinoid Preparations.*

Internationally, private companies have completed clinical studies and successfully marketed standardized *Cannabis* products (Cannabis flowers, extracts, and nabiximols) in 27 countries. In the last decade, the U.S. has approved over 550 studies of marijuana or *Cannabis*, 144 with dronabinol or tetrahydrocannabinol (THC), and 96 with pure CBD or a CBD-rich *Cannabis* extract according to clinicaltrials.gov.

Cannabis is dispensed in pharmacies throughout Europe and at dispensaries in the U.S., which conforms to standards that would qualify the *Cannabis* products as botanical medicines based on existing safety guidelines from the FDA, AHP, and the U.S. Department of Agriculture (USDA). The quality and safety of medical *Cannabis* and its derivatives are adequately addressed by existing national and local standards. The standards also address best practices for *Cannabis* operations, such as manufacturers, cultivation sites, laboratories, and dispensaries. Botanical medicines and herbal products are regulated; many of these botanical safety standards are directly applied to medical *Cannabis.* Several countries have made significant regulatory efforts to enact the existing national and local level standards for *Cannabis* production and distribution[57,214,543].

Some countries have published monographs (i.e., Czech Republic, Holland, U.S., and Canada) to specifically address the quality control of *Cannabis*, including methodology. Trade associations have published best practices for cultivation, dispensing, manufacturing and laboratory practices[544]. Furthermore, an abundance of national and international guidance documents provide quality control standards that address nearly every aspect of quality control and product safety for botanical substances, such as *Cannabis* and its derivatives.

One hurdle to quality control of medical *Cannabis* products is the present control status of *Cannabis* in countries such as the U.S. and also the controls under the conventions. National and international controls prevent adequate product testing in U.S. *Cannabis* programs and may inadvertently jeopardize public health. There has only been a single study, which examined the labeling accuracy (i.e., potency) of the *Cannabis* products' accessed through three state programs in the U.S. The study demonstrateed that medical *Cannabis* product labels in the U.S. can be inaccurate [545]. However, the study also demonstrated that the current national controls for *Cannabis* impair the ability to address *Cannabis* product public health concerns.

The DEA controls the release of analytical-quality standards for calibrating scientific instruments, which can only be purchased in necessary amounts if the operation has received a Schedule I license from the DEA. The DEA *will not grant* a Schedule I license to a state sponsored medical *Cannabis* laboratory, because the laboratory would receive medical *Cannabis* samples for analysis from *non*-DEA licensed sources (such as State licensed manufacturers, distribution centers, cultivation sites, patients, or doctors that recommend *Cannabis* to patients). Therefore, the Schedule I status of *Cannabis* blocks most laboratories from determining the precise potency of the product. It is difficult to address public health issues regarding medical *Cannabis* products while it remains in Schedule I status. However, testing for clinically relevant contaminants – such as heavy metals, bacteria, and fungus – can proceed without requiring DEA licensing but this product safety testing is also vulnerable to DEA or federal interference due to the scheduling status.

A normalizing factor for a medicine like *Cannabis* in the U.S. could be for the USP to create a *Cannabis* monograph; these standards would be adopted to regulate *Cannabis* as a medicinal product nationally[546]. However, this action would grant pharmacists in the U.S. the ability to work with *Cannabis*, which is forbidden by the DEA. Hence, the USP *cannot* create a *Cannabis* monograph and still maintain compliance with the DEA.

Presently, the USP defers to the AHP monograph as the current standard for *Cannabis* products in the U.S.[7]. A recent meeting of the USP suggests drafting of the document will not begin until *Cannabis* is rescheduled to a status that recognizes its medicinal use and outstanding safety profile. The standards issued by the AHP monograph and American Herbal Products Association (AHPA) have been adopted by 16 U.S. states to regulate product safety for their medical *Cannabis* programs. Furthermore, AHPA, the trade association for the herbal products industry, has issued its medical marijuana manufacturing guidelines, completing its series of recommendations for state regulators in the areas of manufacturing, packaging and labeling, cultivation, dispensary operations, and laboratory practices.

Another example of production with good quality assurance/quality control is the Dutch program for

medicinal *Cannabis*. This is produced under responsibility of the Ministry of Health and meets a number of quality requirements: consistent strength on THC and composition of secondary cannabinoids, absence of microbiological contamination, pesticides and heavy metals, and humidity. Where there is a norm provided in the European Pharmacopoeia, this norm is followed[547].

The next sections briefly discuss published resources and guidance documents being used by governments to provide quality control and product safety around the world for agricultural products and botanical medicines, including *Cannabis*.

Good Agricultural and Collection Practices

The quality of raw material for botanical medicine can be safeguarded by using Good Agricultural and Collection Practices (GACP aka GAP) to the extent possible in all aspect of growing, harvesting, and storage[548]. Specific guidelines for regulators regarding *Cannabis* cultivation practices in the U.S. have been published by AHPA. These standards include requirements for standard operating procedure documentation, employee safety training, security, and batch tracking[544]. The American Herbal Pharmacopoeia has also released standards of quality control for *Cannabis* cultivation.

In The Netherlands, Czech Republic, and Italy, *Cannabis* to be used by patients, must be produced under GMP-like conditions. All products have to be fully tested (by an independent laboratory) per batch on cannabinoid content, absence of heavy metals, aflatoxins, pesticides (residue), and microbes to a level of <10 cfu. Standardization of *Cannabis* and *Cannabis* derivatives according to the monograph of herbal medicines of the European Medicine Agency (EMA) is mandatory and has to be proven for each batch.

In Austria (AGES) and the UK (GW Pharmaceuticals Ltd), *Cannabis* has to be produced under GAP; however, the derivatives from this *Cannabis* must be produced under GMP. Finished products need to be standardized according to regular [pharmaceutical] products.

Good Manufacturing Practice for Cannabis

Many guidance documents are available for reference and use in the manufacturing of plant medicines and products, any facility manufacturing products for human consumption should follow GMP. WHO has published guidelines on manufacturing botanical and herbal medicines, and the U.S. FDA has published guidance documents as well[549-552]. The AHPA manufacturing guidelines have a specific procedure for the recall of medical *Cannabis* products that do not meet "appropriate standards of identity, purity, strength, and composition and their freedom from contamination or adulteration." The AHP *Cannabis* monograph also sets limits for residues such as solvents and pesticides, heavy metals, bacteria, and fungi[214].

Good Laboratory Practices

Methods used to determine potency should be scientifically validated by laboratories for several criteria including but not limited to specificity, linearity, accuracy, precision, and ruggedness. The FDA and other organizations (i.e., AHPA, USP, and AHP) have provided guidance documents that represent the current thinking on method validation and other aspects of good laboratory practices. There are also

international standards for analyzing medical *Cannabis* products, which have been issued, for example, by the UN's Office of Drugs and Crime in their document entitled "Recommended Methods for the Identification and Analysis of *Cannabis* and *Cannabis* products"[553].

Below are a few examples of applicable guidance from a regulatory perspective, for analytical method validation for new methods, or methods not outlined in existing international and national regulatory documents:

- USP–NF, Validation of Compendial Methods; USP pharmacopeia 35, United States Pharmacopeia Convention, Inc., Rockville, MD. May 1, 2012 – December 1, 2012.
- U.S. FDA, Center for Drug Evaluation and Research (CDER), Reviewer Guidance on Validation of Chromatographic Methods, November 1994.
- American Herbal Pharmacopoeia *Cannabis Inflorescence*. Standards of Identity, Analysis, and Quality Control (2013).

Quality control and quality standards for medicinal *Cannabis* have been developed and adopted by over 16 U.S. states, and many countries such as Canada, Israel, the Netherlands, and the Czech Republic to name a few. The current standards are presently being appropriately applied or implemented through third party licensed certification bodies, for regulating *Cannabis* and *Cannabis*-related products for human consumption.

The adopted product safety standards require *Cannabis* operations to implement quality control/quality assurance programs, batch tracking, adverse event tracking, employee safety training, and documentation of all relevant operational procedures, among several other criteria. The AHP and AHPA documents point to Patient Focused Certification (PFC) for implementation of these standards. PFC has offices in Washington, DC and the Czech Republic. PFC is the only international program that can verify that a country, region or state's *Cannabis* standards are being followed (www.patientfocusedcertification.com). PFC conducts a physical (site or facility) and documentation audit of the operation to generate an audit report that is submitted to a review board. PFC's review board features experts that have served in regulatory and scientific roles in U.S. presidential administrations, at the USDA, in quality control laboratories, and related disciplines. PFC audited its first *Cannabis* operations in the U.S. in 2013 and in Europe in 2015, and is now an option for regulators in every country, state, or region with medical *Cannabis* access programs.

A successful public health outcome of product safety regulations has been demonstrated through successful product recalls in Canada and the U.S. This required the cooperation of government, manufacturers, and 3rd party certifying bodies that resulted in consumer protection[554-560].

To address public health concerns regarding the increasing availability of medical *Cannabis* products, the scheduling status of *Cannabis* needs to be thoughtfully and deliberately rescheduled, in order for producers, cultivators, manufacturers, laboratories, clinicians, researchers, and regulators to fully implement quality control standards for medical *Cannabis* products. Additionally, the UN Conventions allow for governments to issue multiple licenses to cultivate or produce *Cannabis.*

(2) THERE ARE ADEQUATE SAFETY STUDIES.

Cannabis products have been on the market for decades and have shown acceptable safety standards for use under medical supervision. Smoked, vaporized, or ingested marijuana can deliver consistent amounts of active chemicals and a toxic lethal overdose of *Cannabis* is not achievable.

Sixteen states have adopted the national standards and guidance provided by the AHPA Cannabis Best Practices documents and the *American Herbal Pharmacopoeia Cannabis Inflorescence Standards of Identity, Analysis, and Quality Control monograph*. Federal standards are not available for *Cannabis* and will not be produced by the USP while the plant is Schedule I because the USP would fall out of compliance with Drug Enforcement Administration (DEA) standards. The FDA has approved several *Cannabis* studies and a new IND program with a *Cannabis* extract (marketed as Epidiolex) that is currently being administered to children in hospitals across the U.S.

While street marijuana has a high potential for abuse, standardized *Cannabis* products do not have a high potential of abuse, have been on the market for decades in the U.S. (Marinol and Nabilone), and whole-plant *Cannabis* medicines are available in 27 other countries (Bedrocan and Nabiximols) [60]. Commonsense dictates that self-administration with unstandardized street drugs has a high potential for abuse but the data addressing *Cannabis* does not report or document nor support the notion of significant abuse or divergence with standardized *Cannabis* products. *Cannabis* should be rescheduled because standardized preparations have a well-documented low potential for abuse and a low street value or resale value.

Summaries on the toxicology of *Cannabis* are listed below. For references on human toxicology research and *Cannabis* please visit (http://american-safe-access.s3.amazonaws.com/criticalreviewFINAL.pdf):

- Based on current understanding of basic toxicity research – sedation, cytotoxicity, genotoxicity, etc. – *Cannabis* and its components seem to have a uniquely wide safety margin[36-39]. To date, there has never been a single well-documented case of human fatality attributable to an overdose of *Cannabis* or its components, and no experimental or non-extrapolated LD_{50} can be attributed to a toxic or lethal overdose of *Cannabis* or a preparation thereof.

- No scientifically significant negative neuropsychological sequelae have yet been attributable to *Cannabis* usage. Arguably, some of these studies remain limited by a number of factors that need to be controlled in future investigations. Primarily, *Cannabis* use and dosing needs to be confirmed in users with biological and chemical tests, as issues of dosing and patterns of use are confounding factors when not adjusted for. The meta-analytical study of long-term *Cannabis* use on neurocognitive functioning, results failed to find any substantial, systematic effect on users who were not concurrently intoxicated.

- Claims of brain damage and cerebral atrophy are not supported by current evidence. When controlling for pertinent variables such as age, gender, and history of alcohol use, research has not

been able to show any association between the use of *Cannabis* and changes in brain structures[59].

- Short-term use of existing standardized medical *Cannabis* and *Cannabis* products appear to increase the risk of non-serious adverse events. Risks associated with long-term *Cannabis* use are poorly characterized in published clinical trials and observational studies; however, the cognitive effects observed in long-term users do not appear to be permanent in nature[40]. With the exception of very limited studies on synthetic endocannabinoid system modulators, *Cannabis* medicines do not appear to cause significant serious adverse events.

(3) THERE ARE ADEQUATE AND WELL-CONTROLLED STUDIES PROVING EFFICACY.

To date, more than 30,000 modern peer-reviewed scientific articles on the chemistry and pharmacology of *Cannabis* and the cannabinoids have been published, and more than 1,500 articles investigating the body's natural endocannabinoids are published every year. In recent years, modern gold-standard placebo-controlled human trials have also been conducted.

At the time of writing this document, according to clinicaltrials.gov, there are hundreds of approved human research studies. These studies are currently either completed, recruiting, approved, or in process. A total of 144 are approved for THC, 96 are approved for CBD, and 559 are approved for marijuana or *Cannabis.* Due to Schedule I status, medical *Cannabis* preparations such as nabiximols and CBD-rich extracts are imported and cannot be manufactured in the U.S., even though they are licensed pharmaceutical products.

There is a wealth of clinical information available on the uses of standardized medical *Cannabis* products. The FDA has approved new drug applications for *Cannabis* products. For example, a CBD-rich extract (marketed as Epidiolex) is an imported, purified *Cannabis* extract that has been approved for clinical use in children and is currently in clinical practice across several institutions in the U.S. Additionally, an inhaled *Cannabis* study has recently been approved for investigating therapeutic effects in PTSD.

Cannabis currently has accepted medical uses in 41 states and the District of Columbia. *Cannabis* and its products have mandatory testing requirements. A *Cannabis* nabiximol, a whole-plant ethanolic extract, has generated more than 9,000 patient/years of modern clinical data for the treatment of chronic pain[126].

> A 2009 review of clinical studies conducted over a 38-year period found that "nearly all of the 33 published controlled clinical trials conducted in the U.S. have shown significant and measurable benefits in subjects receiving the treatment[148]." The review's authors made particular effort to note that cannabinoids have the capacity for analgesia through neuromodulation in ascending *and* descending pain pathways, neuroprotection, and by anti-inflammatory mechanisms – all of which indicate that the cannabinoids found in *Cannabis* have applications in significantly managing chronic pain, muscle spasticity, cachexia, and other variously debilitating conditions.

Currently, *Cannabis* is most often recommended as a complementary or adjunctive medicine. However, there exists a substantial consensus amongst experts in the relevant disciplines – including the American

College of Physicians – that *Cannabis* and cannabinoid-based medicines have undeniable therapeutic properties that could potentially treat a variety of serious and chronic illnesses.

(4) THE DRUG IS ACCEPTED BY QUALIFIED EXPERTS.

In this document, under the section entitled "List of Medical and Scientific Organizations that have Issued Letter of Support for Medical Cannabis" are over 200 medical, scientific, health professionals, religious and community organizations who accept *Cannabis* as a medicine and have issued letters in support of this medicine (http://www.medicalcannabis.com/about/health-care-professionals/supporting-organizations/)

Medical schools are teaching required coursework which includes the endocannabinoid system and the therapeutic applications of *Cannabis.* For example, theanswerpage.org, a Harvard University based CME, is educating physicians about the benefits of the medical uses of *Cannabis*. This has led to the creation of clinical *Cannabis* certification for physicians; an educational program that is required for physicians to recommended medical cannabis in states such programs (http://cannabiscarecertification.org).

(5) THE SCIENTIFIC EVIDENCE IS WIDELY AVAILABLE.

One of the criteria preventing the rescheduling of *Cannabis* is the notion that information about this medicine is not widely available. There are tens of thousands of peer reviewed articles available through online portals, journal websites, and other resources for health professionals to access clinical information about *Cannabis,* including but not limited to: Springer, Wiley, Pubmed, Public Libraries, medical and graduate school libraries, and websites of expert groups such as Americans for Safe Access, theAnswerpage.org, and the International Cannabis and Cannabinoid Institute.

The Internet has also revolutionized research and science by allowing the generation of and access to large amounts of information that would have previously been nearly impossible to obtain. People across the globe can now access hordes (a search for 'cannabis research' through web of science yields 120,000 articles) of previously unavailable scientific and clinical information.

REFERENCES:

[1] 2016, "Allow Marijuana for Vets with Ptsd, U.S. Voters Say 10-1, Quinnipiac University National Poll Finds; Slim Majority Says Legalize Marijuana in General ," qu.edu [Online]. Available: https://www.qu.edu/images/polling/us/us06062016_Unru52x.pdf. [Accessed: 20-Jun-2016].

[2] 2015, "www.warren.senate.gov/files/documents/HHS_ONDCP_DEA_Marijuana_letter.pdf," warren.senate.gov [Online]. Available: http://www.warren.senate.gov/files/documents/HHS_ONDCP_DEA_Marijuana_letter.pdf. [Accessed: 20-Jun-2016].

[3] 2011, "Bi-Coastal Governors Petition Federal Government to Reclassify Marijuana for Medical Use."

[4] Woodward, C., 1937, "Statement of Dr. William C Woodward, Legislative Council, American Medical Association, before the House of Representatives, Committee on Ways and Means, May 4, 1937. Dr. Woodard told Congress that" The American Medical Association knows of no evidence that marijuana is a dangerous drug," and warned that a prohibition' loses sight of the fact that future investigation may show that there are substantial medical uses for cannabis.'."

[5] Chafee, L., and Gregoire, C., "Rulemaking petition to reclassify cannabis for medical use from a Schedule I controlled substance to a Schedule II," digitalarchives.wa.gov.

[6] Pascual, K., 2016, "DEA May Downgrade Marijuana From Schedule 1 Drug," Tech Times [Online]. Available: http://www.techtimes.com/articles/147969/20160407/dea-may-downgrade-marijuana-from-schedule-1-drug.htm. [Accessed: 06-Jun-2016].

[7] Ahing, A. A., 2016, "USP Medical Cannabis Roundtable Briefing," United States Pharmacoepia, pp. 1–13.

[8] Hall, W., and Solowij, N., 1998, "Adverse effects of cannabis," The Lancet, **352**(9140), pp. 1611–1616.

[9] Wang, T., Collet, J.-P., Shapiro, S., and Ware, M. A., 2008, "Adverse effects of medical cannabinoids: a systematic review.," CMAJ, **178**(13), pp. 1669–1678.

[10] Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A., and Yurgelun-Todd, D., 2002, "Cognitive Measures in Long-Term Cannabis Users," The Journal of Clinical Pharmacology, **42**(S1), pp. 41S–47S.

[11] Mokrysz, C., Landy, R., Gage, S. H., Munafò, M. R., Roiser, J. P., and Curran, H. V., 2016, "Are IQ and educational outcomes in teenagers related to their cannabis use? A prospective cohort study.," J. Psychopharmacol. (Oxford), **30**(2), pp. 0269881115622241–168.

[12] Yücel, M., Lorenzetti, V., Suo, C., Zalesky, A., Fornito, A., Takagi, M. J., Lubman, D. I., and Solowij, N., 2016, "Hippocampal harms, protection and recovery following regular cannabis use.," Transl Psychiatry, **6**(1), p. e710.

[13] Patton, G. C., Coffey, C., Carlin, J. B., Degenhardt, L., Lynskey, M., and Hall, W., 2002, "Cannabis use and mental health in young people: cohort study," BMJ, **325**(7374), pp. 1195–1198.

[14] Aaltonen, N., Riera Ribas, C., Lehtonen, M., Savinainen, J. R., and Laitinen, J. T., 2014, "Brain regional cannabinoid CB1 receptor signalling and alternative enzymatic pathways for 2-arachidonoylglycerol generation in brain sections of diacylglycerol lipase deficient mice.," Eur J Pharm Sci, **51**, pp. 87–95.

[15] Onaivi, E. S., Ishiguro, H., Gong, J.-P., Patel, S., Meozzi, P. A., Myers, L., Perchuk, A., Mora, Z., Tagliaferro, P. A., Gardner, E., Brusco, A., Akinshola, B. E., Hope, B., Lujilde, J., Inada, T., Iwasaki, S., Macharia, D., Teasenfitz, L., Arinami, T., and Uhl, G. R., 2008, "Brain neuronal CB2 cannabinoid receptors in drug abuse and depression: from mice to human subjects.," PLoS ONE, **3**(2), pp. e1640–e1640.

[16] Xi, Z.-X., Peng, X.-Q., Li, X., Song, R., Zhang, H.-Y., Liu, Q.-R., Yang, H.-J., Bi, G.-H., Li, J., and Gardner, E. L., 2011, "Brain cannabinoid CB2 receptors modulate cocaine's actions in mice," Nat. Neurosci., **14**(9), pp. 1160–1166.

[17] McAllister, W. B., 1991, "Conflicts of Interest in the International Drug Control System," Journal of Policy History, **3**(04), pp. 143–166.

[18] Walker, W. O., 1996, Drugs in the Western Hemisphere: An odyssey of cultures in conflict.

[19] Bauer, H. H., 2015, "How Medical Practice Has Gone Wrong: Causes of the Lack-of-Reproducibility Crisis in Medical Research," Journal of Controversies in Biomedical Research, **1**(1), pp. 28–39.

[20] McLaughlin, P. J., 2012, "Reports of the death of CB1 antagonists have been greatly exaggerated," Behavioural Pharmacology, **23**(5 and 6), pp. 537–550.

[21] Russo, E. B., 2007, "History of Cannabis and Its Preparations in Saga, Science, and Sobriquet," Chemistry & Biodiversity, **4**(8), pp. 1614–1648.

[22] Couchman, J. R., 2014, "Peer review and reproducibility. Crisis or time for course correction?," J. Histochem. Cytochem., **62**(1), pp. 9–10.

[23] Haug, C. J., 2015, "Peer-Review Fraud--Hacking the Scientific Publication Process.," N. Engl. J. Med., **373**(25), pp. 2393–2395.

[24] Begley, C. G., and Ioannidis, J. P. A., 2015, "Reproducibility in science: improving the standard for basic and preclinical research.," Circulation Research, **116**(1), pp. 116–126.

[25] McAllister, S. D., Chan, C., Taft, R. J., Luu, T., Abood, M. E., Moore, D. H., Aldape, K., and Yount, G., 2005, "Cannabinoids selectively inhibit proliferation and induce death of cultured human glioblastoma multiforme cells," J Neurooncol, **74**(1), pp. 31–40.

[26] van den Heuvel, M. J., Clark, D. G., Fielder, R. J., Koundakjian, P. P., Oliver, G. J. A., Pelling, D., Tomlinson, N. J., and Walker, A. P., 1990, "The international validation of a fixed-dose procedure as an alternative to the classical LD50 test," Food and Chemical Toxicology, **28**(7), pp. 469–482.

[27] Mikuriya, T. H., 1969, Historical aspects of cannabis sativa in western medicine, New Physician.

[28] 1968, "Marihuana and society," JAMA: The Journal of the American Medical Association, **204**(13), pp. 1181–1182.

[29] Loewe, S., 1946, "Studies on the pharmacology and acute toxicity of compounds with marihuana activity.," Journal of Pharmacology and Experimental Therapeutics, **88**(2), pp. 154–161.

[30] Loewe, S., 1950, "The active principles of cannabis and the pharmacology of the cannabinols," Archiv fur Experim Pathologie und Pharmakologie.

[31] Grinspoon, L., and Bakalar, J. B., 1997, "Marihuana, the forbidden medicine."

[32] Young, F. L., 1988, In the matter of marijuana rescheduling petition, Drug Enforcement Agency.

[33] Randall, R. C., 1991, Muscle Spasm, Pain & Marijuana Therapy: Testimony from Federal and State Court Proceedings on Marijuana's Medical Use in the Treatment of Multiple ….

[34] Glass, M., Dragunow, M., and Faull, R. L., 1997, "Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain.," NSC, **77**(2), pp. 299–318.

[35] Herkenham, M., Lynn, A. B., Little, M. D., Johnson, M. R., Melvin, L. S., de Costa, B. R., and Rice, K. C., 1990, "Cannabinoid receptor localization in brain.," Proc. Natl. Acad. Sci. U.S.A., **87**(5), pp. 1932–1936.

[36] Speijers, G., Bottex, B., Dusemund, B., Lugasi, A., Tóth, J., Amberg Müller, J., Galli, C. L., Silano, V., and Rietjens, I. M. C. M., 2010, "Safety assessment of botanicals and botanical preparations used as ingredients in food supplements: Testing an European Food Safety Authority-tiered approach," Molecular Nutrition & Food Research, **54**(2), pp. 175–185.

[37] Shelef, A., Barak, Y., Berger, U., Paleacu, D., Tadger, S., Plopsky, I., and Baruch, Y., 2016, "Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study.," J. Alzheimers Dis.

[38] Ware, M. A., and Tawfik, V. L., 2005, "Safety issues concerning the medical use of cannabis and cannabinoids.," Pain Res Manag, **10 Suppl A**, pp. 31A–7A.

[39] Ware, M. A., Wang, T., Shapiro, S., Collet, J.-P., COMPASS study team, 2015, "Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS).," J Pain, **16**(12), pp. 1233–1242.

[40] Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A., and Yurgelun-Todd, D., 2001, "Neuropsychological performance in long-term cannabis users.," Arch. Gen. Psychiatry, **58**(10), pp. 909–915.

[41] Grant, I., and Cahn, B. R., 2005, "Cannabis and endocannabinoid modulators: Therapeutic promises and challenges," Clinical Neuroscience Research, **5**(2-4), pp. 185–199.

[42] Rubin, V., 1975, Cannabis and Culture, Walter de Gruyter, Berlin, New York.

[43] Kokkevi, A., and Dornbush, R., 1977, "Psychological test characteristics of long-term hashish users," Hashish: Studies of long-term use, **1**(3-4), pp. 43–47.

[44] Carter, W. E., 1980, Cannabis in Costa Rica.

[45] Fletcher, J. M., 1996, "Cognitive Correlates of Long-term Cannabis Use in Costa Rican Men," Arch. Gen. Psychiatry, **53**(11), pp. 1051–1057.

[46] Morgan, J. P., and Zimmer, L., 1997, "Marijuana myths, marijuana facts: A review of the scientific evidence," New York: The Lindesmith Center.

[47] Lyketsos, C. G., Garrett, E., Liang, K. Y., and Anthony, J. C., 1999, "Cannabis use and cognitive decline in persons under 65 years of age.," American Journal of Epidemiology, **149**(9), pp. 794–800.

[48] Solowij, N., 1998, Cannabis and cognitive functioning, International research monographs in the addictions, Cambridge.

[49] Solowij, N., and Grenyer, B., 2013, "Long term effects of cannabis on psyche and cognition," Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential, Cannabis and cannabinoids.

[50] Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., McDonald, K., Ward, A., Poulton, R., and Moffitt, T. E., 2012, "Persistent cannabis users show neuropsychological decline from childhood to midlife.," Proceedings of the National Academy of Sciences, **109**(40), pp. E2657–64.

[51] Schreiner, A. M., and Dunn, M. E., 2012, "Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: A meta-analysis.," Experimental and Clinical Psychopharmacology, **20**(5), pp. 420–429.

[52] Solowij, N., Stephens, R. S., Roffman, R. A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., and Vendetti, J., 2002, "Cognitive Functioning of Long-term Heavy Cannabis Users Seeking Treatment," JAMA, **287**(9), pp. 1123–1131.

[53] Kuehnle, J., Mendelson, J. H., Davis, K. R., and New, P. F. J., 1977, "Computed Tomographic Examination of Heavy Marijuana Smokers," JAMA, **237**(12), pp. 1231–1232.

[54] Campbell, A. M. G., Evans, M., Thomson, J. L. G., and Williams, M. J., 1971, "CEREBRAL ATROPHY IN YOUNG CANNABIS SMOKERS," The Lancet, **298**(7736), pp. 1219–e2.

[55] Co, B. T., Goodwin, D. W., Gado, M., Mikhael, M., and Hill, S. Y., 1977, "Absence of cerebral atrophy in chronic cannabis users. Evaluation by computerized transaxial tomography.," JAMA, **237**(12), pp. 1229–1230.

[56] Hannerz, J., and Hindmarsh, T., 1983, "Neurological and neuroradiological examination of chronic cannabis smokers.," Annals of Neurology, **13**(2), pp. 207–210.

[57] Russo, E., Mathre, M. L., Byrne, A., Velin, R., Bach, P. J., Sanchez Ramos, J., and Kirlin, K. A., 2002, "Chronic Cannabis Use in the Compassionate Investigational New Drug Program," Journal of Cannabis therapeutics, **2**(1), pp. 3–57.

[58] Block, R. I., O'Leary, D. S., Ehrhardt, J. C., Augustinack, J. C., Ghoneim, M. M., Arndt, S., and Hall, J. A., 2000, "Effects of frequent marijuana use on brain tissue volume and composition," Neuroreport, **11**(3), pp. 491–496.

[59] Weiland, B. J., Thayer, R. E., Depue, B. E., Sabbineni, A., Bryan, A. D., and Hutchison, K. E., 2015, "Daily marijuana use is not associated with brain morphometric measures in adolescents or adults.," Journal of Neuroscience, **35**(4), pp. 1505–1512.

[60] Robson, P., 2011, "Abuse potential and psychoactive effects of δ-9-tetrahydrocannabinol and cannabidiol oromucosal spray (Sativex), a new cannabinoid medicine," Expert Opin. Drug Saf., **10**(5), pp. 675–685.

[61] Kendler, K. S., and Prescott, C. A., 2014, "Cannabis Use, Abuse, and Dependence in a Population-Based Sample of Female Twins," American Journal of Psychiatry, **155**(8), pp. 1016–1022.

[62] Robson, P. J., 2014, "Therapeutic potential of cannabinoid medicines," Drug Test. Analysis, **6**(1-2), pp. 24–30.

[63] Levin, F. R., Mariani, J. J., Brooks, D. J., Pavlicova, M., Cheng, W., and Nunes, E. V., 2011, "Dronabinol for

the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial," Drug and Alcohol Dependence, **116**(1-3), pp. 142–150.

[64] Schoedel, K. A., Chen, N., Hilliard, A., White, L., Stott, C., Russo, E., Wright, S., Guy, G., Romach, M. K., and Sellers, E. M., 2011, "A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use," Hum. Psychopharmacol. Clin. Exp., **26**(3), pp. n/a–n/a.

[65] Haney, M., Malcolm, R. J., Babalonis, S., Nuzzo, P. A., Cooper, Z. D., Bedi, G., Gray, K. M., McRae-Clark, A., Lofwall, M. R., Sparenborg, S., and Walsh, S. L., 2015, "Oral Cannabidiol does not Alter the Subjective, Reinforcing or Cardiovascular Effects of Smoked Cannabis," pp. 1–31.

[66] Pacher, P., Pacher, P., Bátkai, S., Bátkai, S., Kunos, G., and Kunos, G., 2006, "The Endocannabinoid System as an Emerging Target of Pharmacotherapy," Pharmacological Reviews, **58**(3), pp. 389–462.

[67] McPartland, J. M., Duncan, M., Di Marzo, V., and Pertwee, R. G., 2015, "Are cannabidiol and Δ(9) - tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review.," British Journal of Pharmacology, **172**(3), pp. 737–753.

[68] Abraham, J., 2009, "International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use," Handbook of Transnational Economic Governance Regimes, Brill, pp. 1041–1054.

[69] Baber, N., 2012, "International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH).," British Journal of Clinical Pharmacology, **37**(5), pp. 401–404.

[70] Fescharek, R., K bler, J. R., Elsasser, U., Frank, M., and G thlein, P., 2004, "Medical Dictionary for Regulatory Activities (MedDRA)*," International Journal of Pharmaceutical Medicine, **18**(5), pp. 259–269.

[71] Administration, U. F. A. D., 2007, Medical Dictionary for Regulatory Activities [MedDRA Web site].

[72] Ashton, C. H., 1999, "Adverse effects of cannabis and cannabinoids.," British Journal of Anaesthesia, **83**(4), pp. 637–649.

[73] Campbell, F. A., Tramèr, M. R., Carroll, D., Reynolds, D. J., Moore, R. A., and McQuay, H. J., 2001, "Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review.," BMJ, **323**(7303), pp. 13–16.

[74] By Reuters, "French Drug Trial Disaster Leaves One Brain Dead, Five Injured," NY Times.

[75] Knopf, A., 2016, "Drug trial of cannabinoid painkiller in France results in brain damage, death," Alcoholism & Drug Abuse Weekly, **28**(4), pp. 1–3.

[76] By The Associated Press, "Man Dies After Taking Part in Botched French Clinical Trial," NY Times.

[77] Pacher, P., and Kunos, G., 2013, "Modulating the endocannabinoid system in human health and disease – successes and failures," FEBS Journal, **280**(9), pp. 1918–1943.

[78] Marcu, J. P., and Schechter, J. B., 2015, Chapter 66 - Molecular Pharmacology of CB1 and CB2 Cannabinoid Receptors, Elsevier Inc.

[79] Abrams, D. I., Vizoso, H. P., Shade, S. B., Jay, C., Kelly, M. E., and Benowitz, N. L., 2007, "Vaporization as a smokeless cannabis delivery system: a pilot study.," Clin Pharmacol Ther, **82**(5), pp. 572–578.

[80] Hazekamp, A., Ruhaak, R., Zuurman, L., van Gerven, J., and Verpoorte, R., 2006, "Evaluation of a vaporizing device (Volcano®) for the pulmonary administration of tetrahydrocannabinol," J Pharm Sci, **95**(6), pp. 1308–1317.

[81] Hashibe, M., Morgenstern, H., Cui, Y., Tashkin, D. P., Zhang, Z. F., Cozen, W., Mack, T. M., and Greenland, S., 2006, "Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study," Cancer Epidemiology Biomarkers & Prevention, **15**(10), pp. 1829–1834.

[82] McPartland, J. M., 2008, "Adulteration of cannabis with tobacco, calamus, and other cholinergic compounds," Cannabinoids.

[83] McPartland, J. M., 1994, "Microbiological contaminants of marijuana," Journal of the International Hemp Association.

[84] Calhoun, S. R., Galloway, G. P., and Smith, D. E., 1998, "Abuse potential of dronabinol (Marinol).," Journal of Psychoactive Drugs, **30**(2), pp. 187–196.

[85] Levinthal, C. F., 2010, Drugs, Behavior, and Modern Society, Pearson College Division.

[86] Pendergraft, W. F., Herlitz, L. C., Thornley-Brown, D., Rosner, M., and Niles, J. L., 2014, "Nephrotoxic Effects of Common and Emerging Drugs of Abuse.," Clin J Am Soc Nephrol, **9**(11), pp. 1996–2005.

[87] Nutt, D., 2009, "Estimating drug harms: a risky business," London: Centre for Crime and Justice Studies.

[88] Nutt, D., King, L. A., Saulsbury, W., and Blakemore, C., 2007, "Development of a rational scale to assess the harm of drugs of potential misuse," The Lancet, **369**(9566), pp. 1047–1053.

[89] Nutt, D. J., King, L. A., and Phillips, L. D., 2010, "Drug harms in the UK: a multicriteria decision analysis," The Lancet, **376**(9752), pp. 1558–1565.

[90] Gable, R. S., 2004, "Comparison of acute lethal toxicity of commonly abused psychoactive substances," Addiction, **99**(6), pp. 686–696.

[91] Grant, I., Atkinson, J. H., Gouaux, B., and Wilsey, B., 2012, "Medical marijuana: clearing away the smoke.," Open Neurol J, **6**(1), pp. 18–25.

[92] Guitart, A. M., Bartroli, M., Villalbí, J. R., Guilañá, E., Castellano, Y., Espelt, A., and Brugal, M. T., 2012, "Indicated prevention of problematic drug consumption in adolescents of Barcelona, Spain," Revista Española de Salud Pública, **86**(2), pp. 189–198.

[93] National Institute for Health and clinical Excellence, 2010, "Alcoholuse disorders: preventing the development of hazardous and harmful drinking," NICE Public Health Guidance 24, pp. 1–96.

[94] Crippa, J. A., Zuardi, A. W., Martín-Santos, R., Bhattacharyya, S., Atakan, Z., McGuire, P., and Fusar-Poli, P., 2009, "Cannabis and anxiety: a critical review of the evidence," Hum. Psychopharmacol. Clin. Exp., **24**(7), pp. 515–523.

[95] Crippa, J. A. S., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L., Martin-Santos, R., Simoes, M. V., Bhattacharyya, S., Fusar-Poli, P., Atakan, Z., Filho, A. S., Freitas-Ferrari, M. C., McGuire, P. K., Zuardi, A. W., Busatto, G. F., and Hallak, J. E. C., 2010, "Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report," Journal of Psychopharmacology, **25**(1), pp. 121–130.

[96] Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., de Oliveira, D. C. G., De Martinis, B. S., Kapczinski, F. A. V., Quevedo, J. A. O., Roesler, R., der, N. S. O., Nardi, A. E., n-Santos, R. M. I., Hallak, J. E. C. I. L., Zuardi, A. W., and Crippa, J. E. A. S., 2011, "Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naive Social Phobia Patients," Neuropsychopharmacology, pp. 1–8.

[97] Karniol, I. G., Shirakawa, I., Kasinski, N., Pfeferman, A., and Carlini, E. A., 1974, "Cannabidiol interferes with the effects of Δ9-tetrahydrocannabinol in man," European Journal of Pharmacology, **28**(1), pp. 172–177.

[98] Zuardi, A. W., Shirakawa, I., Finkelfarb, E., and Karniol, I. G., 1982, "Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects," Psychopharmacology, **76**(3), pp. 245–250.

[99] Page, J. B., Fletcher, J., and True, W. R., 1988, "Psychosociocultural Perspectives on Chronic Cannabis Use: The Costa Rican Follow-up," Journal of Psychoactive Drugs, **20**(1), pp. 57–65.

[100] Stefanis, C. N., Dornbush, R. L., and Fink, M., 1977, Hashish: Studies of long-term use.

[101] Fride, E., and Russo, E. B., 2006, "Neuropsychiatry: Schizophrenia, depression, and anxiety," Endocannabinoids: The Brain and Body's Marijuana and Beyond.

[102] Ballard, M. E., Bedi, G., and de Wit, H., 2012, "Effects of delta-9-tetrahydrocannabinol on evaluation of emotional images," J. Psychopharmacol. (Oxford), **26**(10), pp. 1289–1298.

[103] Bergamaschi, M. M., Queiroz, R. H. C., Chagas, M. H. N., Linares, I. M. P., Arrais, K. C., de Oliveira, D. C. G., Queiroz, M. E., Nardi, A. E., Huestis, M. A., Hallak, J. E. C., Zuardi, A. W., Moreira, F. A., and Crippa, J. A. S., 2013, "Rimonabant effects on anxiety induced by simulated public speaking in healthy humans: a preliminary report," Hum. Psychopharmacol. Clin. Exp., **29**(1), pp. 94–99.

[104] Russo, E. B., 2011, "Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," British Journal of Pharmacology, **163**(7), pp. 1344–1364.

[105] Grinspoon, L., and Bakalar, J. B., 2011, "The Use of Cannabis as a Mood Stabilizer in Bipolar Disorder: Anecdotal Evidence and the Need for Clinical Research," http://dx.doi.org/10.1080/02791072.1998.10399687, **30**(2), pp. 171–177.

[106] Bovasso, G. B., 2001, "Cannabis abuse as a risk factor for depressive symptoms," Am J Psychiatry, **158**(12), pp. 2033–2037.

[107] Denson, T. F., and Earleywine, M., 2006, "Decreased depression in marijuana users," Addictive Behaviors, **31**(4), pp. 738–742.

[108] Kedzior, K. K., and Laeber, L. T., 2014, "A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies," BMC Psychiatry, **14**(1), p. 136.

[109] Réus, G. Z., Stringari, R. B., Ribeiro, K. F., Luft, T., Abelaira, H. M., Fries, G. R., Aguiar, B. W., Kapczinski, F., Hallak, J. E., Zuardi, A. W., Crippa, J. A., and Quevedo, J., 2011, "Administration of cannabidiol and imipramine induces antidepressant-like effects in the forced swimming test and increases brain-derived neurotrophic factor levels in the rat amygdala.," Acta Neuropsychiatr, **23**(5), pp. 241–248.

[110] Zanelati, T. V., Biojone, C., Moreira, F. A., Guimarães, F. S., and Joca, S. R. L., 2010, "Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors.," British Journal of Pharmacology, **159**(1), pp. 122–128.

[111] Rylander, M., Valdez, C., and Nussbaum, A. M., 2014, "Does the legalization of medical marijuana increase completed suicide?," The American Journal of Drug and Alcohol Abuse, **40**(4), pp. 269–273.

[112] Anderson, D. M., Rees, D. I., and Sabia, J. J., 2014, "Medical Marijuana Laws and Suicides by Gender and Age," American Journal of Public Health, **104**(12), pp. 2369–2376.

[113] Rasic, D., Weerasinghe, S., Asbridge, M., and Langille, D. B., 2013, "Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students.," Drug and Alcohol Dependence, **129**(1-2), pp. 49–53.

[114] Price, C., Hemmingsson, T., Lewis, G., ZAMMIT, S., and Allebeck, P., 2009, "Cannabis and suicide: longitudinal study.," Br J Psychiatry, **195**(6), pp. 492–497.

[115] Beautrais, A. L., Joyce, P. R., and Mulder, R. T., 1999, "Cannabis abuse and serious suicide attempts," Addiction, **94**(8), pp. 1155–1164.

[116] Calabria, B., Degenhardt, L., Hall, W., and Lynskey, M., 2010, "Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use," Drug and Alcohol Review, **29**(3), pp. 318–330.

[117] van Ours, J. C., Williams, J., Fergusson, D., and Horwood, L. J., 2013, "Cannabis use and suicidal ideation," Journal of Health Economics, **32**(3), pp. 524–537.

[118] Chabrol, H., Chauchard, E., and Girabet, J., 2008, "Cannabis use and suicidal behaviours in high-school students," Addictive Behaviors, **33**(1), pp. 152–155.

[119] Bonn-Miller, M. O., Vujanovic, A. A., Feldner, M. T., Bernstein, A., and Zvolensky, M. J., 2007, "Posttraumatic stress symptom severity predicts marijuana use coping motives among traumatic event-exposed marijuana users," Journal of Traumatic Stress, **20**(4), pp. 577–586.

[120] Douglas, B. J., Southwick, S. M., and Darnell, A., 1996, "Chronic PTSD in Vietnam combat veterans: course of illness and substance abuse," American Journal of ….

[121] Vandrey, R., Babson, K. A., Herrmann, E. S., and Bonn-Miller, M. O., 2014, "Interactions between disordered sleep, post-traumatic stress disorder, and substance use disorders," International Review of Psychiatry, **26**(2), pp. 237–247.

[122] Neumeister, A., Normandin, M. D., Pietrzak, R. H., Piomelli, D., Zheng, M. Q., Gujarro-Anton, A., Potenza, M. N., Bailey, C. R., Lin, S. F., Najafzadeh, S., Ropchan, J., Henry, S., Corsi-Travali, S., Carson, R. E., and Huang, Y., 2013, "Elevated brain cannabinoid CB1 receptor availability in post-traumatic stress disorder: a positron emission tomography study," Molecular Psychiatry, **18**(9), pp. 1034–1040.

[123] Passie, T., EMRICH, H. M., Karst, M., Brandt, S. D., and Halpern, J. H., 2012, "Mitigation of post-traumatic stress symptoms by Cannabis resin: A review of the clinical and neurobiological evidence," Drug Test. Analysis, **4**(7-8), pp. 649–659.

[124] Blake, D. R., ROBSON, P., Ho, M., Jubb, R. W., and McCabe, C. S., 2006, "Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis.," Rheumatology (Oxford), **45**(1), pp. 50–52.

[125] Grant, I., Atkinson, J. H., and Mattison, A., 2010, "Report to the legislature and governor of the state of California presenting findings pursuant to SB847 which created the CMCR and provided state funding," San Diego.

[126] Russo, E. B., and Hohmann, A. G., 2012, "Role of Cannabinoids in Pain Management," Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches, Springer New York, New York, NY, pp. 181–197.

[127] Russo, E., and Guy, G. W., 2006, "A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol," Medical Hypotheses, **66**(2), pp. 234–246.

[128] Gaoni, Y., and Mechoulam, R., 1964, "Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish," J. Am. Chem. Soc., **86**(8), pp. 1646–1647.

[129] Wood, T. B., Spivey, W. T. N., and Easterfield, T. H., 1899, "III.—Cannabinol. Part I," J. Chem. Soc., Trans., **75**(0), pp. 20–36.

[130] Adams, R., Baker, B. R., and Wearn, R. B., 1940, "Structure of Cannabinol. III. Synthesis of Cannabinol, 1-Hydroxy-3-n-amyl-6,6,9-trimethyl-6-dibenzopyran 1," J. Am. Chem. Soc., **62**(8), pp. 2204–2207.

[131] Šantavý, F., 1964, Notes on the structure of cannabidiol compounds, Acta Univ Palacki Olomuc.

[132] Ghosh, R., Todd, A. R., and Wilkinson, S., 1940, "Cannabis indica. Part V. The synthesis of cannabinol," Journal of the Chemical Society (Resumed), (0), pp. 1393–1396.

[133] Kabelik, J., Krejci, Z., and Šantavý, F., 1960, "Cannabis as a medicament," Bull Narc.

[134] Krejci, Z., and Šantavý, F., 1955, "Isolace dalších látek z listí indického konopí Cannabis sativa L. [Isolation of other substances from the leaves of the Indian hemp (Cannabis sativa L., varietas indica.)] ," Acta Univ Palacki Olomuc, **6**, pp. 59–66.

[135] Maccarrone, M., Bab, I., Bíró, T., Cabral, G. A., Dey, S. K., Di Marzo, V., Konje, J. C., Kunos, G., Mechoulam, R., Pacher, P., Sharkey, K. A., and Zimmer, A., 2015, "Endocannabinoid signaling at the periphery: 50 years after THC.," Trends in Pharmacological Sciences, **0**(0), pp. 277–296.

[136] Pertwee, R., 2014, Handbook of Cannabis, Oxford University Press.

[137] Pertwee, R. G., 2015, "Endocannabinoids and Their Pharmacological Actions.," Handb Exp Pharmacol, **231**(Chapter 1), pp. 1–37.

[138] Pertwee, R. G., 2009, "Emerging strategies for exploiting cannabinoid receptor agonists as medicines," British Journal of Pharmacology, **156**(3), pp. 397–411.

[139] Pertwee, R. G., 2005, "Pharmacological Actions of Cannabinoids," Cannabinoids, **168**(Chapter 1), pp.

1–51.

[140] Devane, W. A., Dysarz, F. A., Johnson, M. R., Melvin, L. S., and Howlett, A. C., 1988, "Determination and characterization of a cannabinoid receptor in rat brain.," Molecular Pharmacology, **34**(5), pp. 605–613.

[141] Devane, W. A., Hanuš, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., and Mechoulam, R., 1992, "Isolation and structure of a brain constituent that binds to the cannabinoid receptor," Science, **258**(5090), pp. 1946–1949.

[142] Hanuš, L. O., 2009, "Pharmacological and therapeutic secrets of plant and brain (endo)cannabinoids," Med. Res. Rev., **29**(2), pp. 213–271.

[143] Hanuš, L. O., 2007, "Discovery and Isolation of Anandamide and Other Endocannabinoids," Chemistry & Biodiversity, **4**(8), pp. 1828–1841.

[144] Hanuš, L., Gopher, A., Almog, S., and Mechoulam, R., 1993, "Two new unsaturated fatty acid ethanolamides in brain that bind to the cannabinoid receptor.," J. Med. Chem., **36**(20), pp. 3032–3034.

[145] Mechoulam, R., Ben-Shabat, S., Hanuš, L., Ligumsky, M., Kaminski, N. E., Schatz, A. R., Gopher, A., Almog, S., Martin, B. R., Compton, D. R., Pertwee, R. G., Griffin, G., Bayewitch, M., Barg, J., and Vogel, Z., 1995, "Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors," Biochemical Pharmacology, **50**(1), pp. 83–90.

[146] Hanuš, L., Abu-Lafi, S., Fride, E., Breuer, A., Vogel, Z., Shalev, D. E., Kustanovich, I., and Mechoulam, R., 2001, "2-arachidonyl glyceryl ether, an endogenous agonist of the cannabinoid CB1 receptor.," Proc. Natl. Acad. Sci. U.S.A., **98**(7), pp. 3662–3665.

[147] Russo, E. B., 2008, "Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?," Neuro Endocrinol. Lett., **29**(2), pp. 192–200.

[148] Aggarwal, S. K., Carter, G. T., Sullivan, M. D., ZumBrunnen, C., Morrill, R., and Mayer, J. D., 2009, "Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions.," J Opioid Manag, **5**(3), pp. 153–168.

[149] Doblin, R. E., and Kleiman, M. A., 1991, "Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes.," J. Clin. Oncol., **9**(7), pp. 1314–1319.

[150] Russo, E. B., Burnett, A., Hall, B., and Parker, K. K., 2005, "Agonistic Properties of Cannabidiol at 5-HT1a Receptors," Neurochem. Res., **30**(8), pp. 1037–1043.

[151] Di Marzo, V., Sepe, N., De Petrocellis, L., Berger, A., Crozier, G., Fride, E., and Mechoulam, R., 1998, "Trick or treat from food endocannabinoids?," Nature, **396**(6712), pp. 636–637.

[152] Marcu, J. P., 2015, Chapter 62 - An Overview of Major and Minor Phytocannabinoids, Elsevier Inc.

[153] Console-Bram, L., Marcu, J., and Abood, M. E., 2012, "Cannabinoid receptors: nomenclature and pharmacological principles.," Prog. Neuropsychopharmacol. Biol. Psychiatry, **38**(1), pp. 4–15.

[154] Marcu, J., Shore, D. M., Kapur, A., Trznadel, M., Makriyannis, A., Reggio, P. H., and Abood, M. E., 2013, "Novel insights into CB1 cannabinoid receptor signaling: a key interaction identified between the

extracellular-3 loop and transmembrane helix 2.," J. Pharmacol. Exp. Ther., **345**(2), pp. 189–197.

[155] Balenga, N. A. B., Aflaki, E., Kargl, J., Platzer, W., Schröder, R., Blättermann, S., Kostenis, E., Brown, A. J., Heinemann, A., and Waldhoer, M., 2011, "GPR55 regulates cannabinoid 2 receptor-mediated responses in human neutrophils," Nature Publishing Group, pp. 1–18.

[156] Pertwee, R. G., Howlett, A. C., Abood, M. E., Alexander, S. P. H., Di Marzo, V., Elphick, M. R., Greasley, P. J., Hansen, H. S., Kunos, G., Mackie, K., Mechoulam, R., and Ross, R. A., 2010, "International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands: Beyond CB1 and CB2," Pharmacological Reviews, **62**(4), pp. 588–631.

[157] Ryberg, E., Larsson, N., Sjögren, S., Hjorth, S., Hermansson, N.-O., Leonova, J., Elebring, T., Nilsson, K., Drmota, T., and Greasley, P. J., 2009, "The orphan receptor GPR55 is a novel cannabinoid receptor," British Journal of Pharmacology, **152**(7), pp. 1092–1101.

[158] Andradas, C., Caffarel, M. M., mez, E. P. E. R.-G. O., Salazar, M., Lorente, M., Velasco, G., n, M. G. A., and nchez, C. S. A., 2010, "The orphan G protein-coupled receptor GPR55 promotes cancer cell proliferation via ERK," Oncogene, pp. 1–8.

[159] Di Marzo, V., and Piscitelli, F., 2015, "The Endocannabinoid System and its Modulation by Phytocannabinoids.," Neurotherapeutics, **12**(4), pp. 692–698.

[160] "Joy JE. Op Cit."

[161] Mechoulam, R., 2005, "Plant cannabinoids: a neglected pharmacological treasure trove," British Journal of Pharmacology, **146**(7), pp. 913–915.

[162] Mechoulam, R., 2006, Cannabinoids as Therapeutics, Springer Science & Business Media, Basel.

[163] ADAMS, I. B., and Martin, B. R., 1996, "Cannabis: pharmacology and toxicology in animals and humans," Addiction, **91**(11), pp. 1585–1614.

[164] Domino, E. E., 1999, "Cannabinoids and the Cholinergic System," Marihuana and Medicine, G.G. Nahas, K.M. Sutin, D. Harvey, S. Agurell, N. Pace, and R. Cancro, eds., Humana Press, Totowa, NJ, pp. 223–226.

[165] McPartland, J. M., and Russo, E. B., 2001, "Cannabis and cannabis extracts: greater than the sum of their parts?," Journal of Cannabis therapeutics, **1**(3-4), pp. 103–132.

[166] Mitchelson, F., 1992, "Pharmacological Agents Affecting Emesis," Drugs, **43**(4), pp. 443–463.

[167] Russo, E. B., Burnett, A., Hall, B., and Parker, K. K., 2005, "Agonistic Properties of Cannabidiol at 5-HT1a Receptors," Neurochem. Res., **30**(8), pp. 1037–1043.

[168] Grotenhermen, F., 2003, "Pharmacokinetics and pharmacodynamics of cannabinoids.," Clin Pharmacokinet, **42**(4), pp. 327–360.

[169] Mattes, R. D., Shaw, L. M., and Engelman, K., 1994, "Effects of cannabinoids (marijuana) on taste intensity and hedonic ratings and salivary flow of adults," Chemical Senses, **19**(2), pp. 125–140.

[170] Committee, S. A. T. S., 1998, Cannabis: the scientific and medical evidence, House of Commons Library Research ….

[171] Joy, J. E., Watson, S. J., Jr, and Benson, J. A., Jr, 1999, Marijuana and Medicine:: Assessing the Science Base, National Academies Press, Washington, D.C.

[172] Pope, H. G., 2002, "Cannabis, cognition, and residual confounding.," JAMA, **287**(9), pp. 1172–1174.

[173] Lambert, D. M., 2001, "[Medical use of cannabis through history].," J Pharm Belg, **56**(5), pp. 111–118.

[174] Pacher, P., 2006, "The Endocannabinoid System as an Emerging Target of Pharmacotherapy," Pharmacological Reviews, **58**(3), pp. 389–462.

[175] Ben Amar, M., 2006, "Cannabinoids in medicine: A review of their therapeutic potential.," Journal of Ethnopharmacology, **105**(1-2), pp. 1–25.

[176] Zuardi, A. W., 2006, "History of cannabis as a medicine: a review," Revista Brasileira de Psiquiatria, **28**(2), pp. 153–157.

[177] Hiley, C. R., and Ford, W. R., 2004, "Cannabinoid pharmacology in the cardiovascular system: potential protective mechanisms through lipid signalling.," Biol Rev Camb Philos Soc, **79**(1), pp. 187–205.

[178] O'Sullivan, S. E., Tarling, E. J., Bennett, A. J., Kendall, D. A., and Randall, M. D., 2005, "Novel time-dependent vascular actions of Delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma.," Biochemical and Biophysical Research Communications, **337**(3), pp. 824–831.

[179] O'Sullivan, S. E., Kendall, D. A., and Randall, M. D., 2004, "Characterisation of the vasorelaxant properties of the novel endocannabinoid N-arachidonoyl-dopamine (NADA).," British Journal of Pharmacology, **141**(5), pp. 803–812.

[180] O'Sullivan, S. E., 2015, "Endocannabinoids and the Cardiovascular System in Health and Disease.," Handb Exp Pharmacol, **231**(Chapter 14), pp. 393–422.

[181] O'Sullivan, S. E., 2014, "Phytocannabinoids and the Cardiovascular System," Handbook of Cannabis, Oxford University Press, pp. 208–226.

[182] Randall, M. D., Kendall, D. A., and O'Sullivan, S., 2004, "The complexities of the cardiovascular actions of cannabinoids.," British Journal of Pharmacology, **142**(1), pp. 20–26.

[183] O'Sullivan, S. E., Randall, M. D., and Gardiner, S. M., 2007, "The in vitro and in vivo cardiovascular effects of Delta9-tetrahydrocannabinol in rats made hypertensive by chronic inhibition of nitric-oxide synthase.," Journal of Pharmacology and Experimental Therapeutics, **321**(2), pp. 663–672.

[184] Stanley, C., and O'Sullivan, S. E., 2014, "Vascular targets for cannabinoids: animal and human studies.," British Journal of Pharmacology, **171**(6), pp. 1361–1378.

[185] Bonnet, U., 2016, "Abrupt Quitting of Long-term Heavy Recreational Cannabis Use is Not Followed by Significant Changes in Blood Pressure and Heart Rate.," Pharmacopsychiatry, (EFirst).

[186] Hancox, R. J., Shin, H. H., Gray, A. R., Poulton, R., and Sears, M. R., 2015, "Effects of quitting cannabis on respiratory symptoms," Eur. Respir. J., **46**(1), pp. ERJ–02289–2014–87.

[187] Abboud, R. T., and Sanders, H. D., 1976, "Effect of oral administration of delta-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects.," Chest, **70**(4), pp. 480–485.

[188] Williams, S. J., Hartlley, J. P. R., and Graham, J. D. P., "Bronchodilator effect of1-tetrahydrocannabinol administered by aerosol to asthmatic patients," Thorax, (31), p. 720.

[189] Tashkin, D. P., Shapiro, B. J., Lee, Y. E., and Harper, C. E., 2015, "Effects of Smoked Marijuana in Experimentally Induced Asthma1, 2," American Review of Respiratory Disease.

[190] Patel, S., Hill, M. N., and Hillard, C. J., 2014, "Effects of Phytocannabinoids on Anxiety, Mood, and the Endocrine System

," Handbook of Cannabis, pp. 189–207.

[191] Holsboer, F., 2000, "The Corticosteroid Receptor Hypothesis of Depression," Neuropsychopharmacology, **23**(5), pp. 477–501.

[192] Ranganathan, M., Braley, G., Pittman, B., Cooper, T., Perry, E., Krystal, J., and D'Souza, D. C., 2008, "The effects of cannabinoids on serum cortisol and prolactin in humans," Psychopharmacologia, **203**(4), pp. 737–744.

[193] Morena, M., Patel, S., Bains, J. S., and Hill, M. N., 2015, "Neurobiological Interactions Between Stress and the Endocannabinoid System," Neuropsychopharmacology, **41**(1), pp. 80–102.

[194] van Leeuwen, A. P., Verhulst, F. C., Reijneveld, S. A., Vollebergh, W. A. M., Ormel, J., and Huizink, A. C., 2011, "Can the gateway hypothesis, the common liability model and/or, the route of administration model predict initiation of cannabis use during adolescence? A survival analysis--the TRAILS study.," J Adolesc Health, **48**(1), pp. 73–78.

[195] Somaini, L., Manfredini, M., Amore, M., Zaimovic, A., Raggi, M. A., Leonardi, C., Gerra, M. L., Donnini, C., and Gerra, G., 2012, "Psychobiological responses to unpleasant emotions in cannabis users.," Eur Arch Psychiatry Clin Neurosci, **262**(1), pp. 47–57.

[196] Zuardi, A. W., Guimarães, F. S., and Moreira, A. C., 1993, "Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers.," Braz. J. Med. Biol. Res., **26**(2), pp. 213–217.

[197] Bonnet, U., 2013, "Chronic Cannabis Abuse, Delta-9-tetrahydrocannabinol and Thyroid Function," Pharmacopsychiatry, **46**(01), pp. 35–36.

[198] Benowitz, N. L., JONES, R. T., and LERNER, C. B., 1976, "Depression of Growth Hormone and Cortisol Response to Insulin-Induced Hypoglycemia After Prolonged Oral Delta-9-Tetrahydrocannabinol Administration in Man," The Journal of Clinical Endocrinology & Metabolism, **42**(5), pp. 938–941.

[199] Lissoni, P., Resentini, M., Mauri, R., Esposti, D., Esposti, G., Rossi, D., Legname, G., and Fraschini, F., 2008, "Effects of Tetrahydrocannabinol on Melatonin Secretion in Man," Hormone and Metabolic Research, **18**(01), pp. 77–78.

[200] Cabral, G. A., Ferreira, G. A., and Jamerson, M. J., 2015, "Endocannabinoids and the Immune System in Health and Disease.," Handb Exp Pharmacol, **231**(Chapter 6), pp. 185–211.

[201] Cabral, G. A., Raborn, E. S., and Ferreira, G. A., 2014, "Phytocannabinoids and the Immune System," Handbook of Cannabis, Oxford University Press, pp. 261–279.

[202] Borrelli, F., Fasolino, I., Romano, B., Capasso, R., Maiello, F., Coppola, D., Orlando, P., Battista, G., Pagano, E., Di Marzo, V., and Izzo, A. A., 2013, "Beneficial effect of the non-psychotropic plant cannabinoid

cannabigerol on experimental inflammatory bowel disease.," Biochemical Pharmacology, **85**(9), pp. 1306–1316.

[203] Correa, F., Docagne, F., Mestre, L., Loría, F., Hernangómez, M., Borrell, J., and Guaza, C., 2007, "Cannabinoid system and neuroinflammation: implications for multiple sclerosis.," Neuroimmunomodulation, **14**(3-4), pp. 182–187.

[204] Formukong, E. A., Evans, A. T., and Evans, F. J., 1988, "Analgesic and antiinflammatory activity of constituents ofCannabis sativa L.," Inflammation, **12**(4), pp. 361–371.

[205] Abrams, D. I., Hilton, J. F., Leiser, R. J., Shade, S. B., Elbeik, T. A., Aweeka, F. T., Benowitz, N. L., Bredt, B. M., Kosel, B., Aberg, J. A., Deeks, S. G., Mitchell, T. F., Mulligan, K., Bacchetti, P., McCune, J. M., and Schambelan, M., 2003, "Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial.," Ann. Intern. Med., **139**(4), pp. 258–266.

[206] Chao, C., Jacobson, L. P., Tashkin, D., Martínez-Maza, O., Roth, M. D., Margolick, J. B., Chmiel, J. S., Rinaldo, C., Zhang, Z.-F., and Detels, R., 2008, "Recreational drug use and T lymphocyte subpopulations in HIV-uninfected and HIV-infected men," Drug and Alcohol Dependence, **94**(1-3), pp. 165–171.

[207] Bredt, B. M., Higuera-Alhino, D., Shade, S. B., Hebert, S. J., McCune, J. M., and Abrams, D. I., 2014, "Short-Term Effects of Cannabinoids on Immune Phenotype and Function in HIV-1-Infected Patients," The Journal of Clinical Pharmacology, **42**(S1), pp. 82S–89S.

[208] ElSohly, M. A., and Slade, D., 2005, "Chemical constituents of marijuana: The complex mixture of natural cannabinoids," Life Sciences, **78**(5), pp. 539–548.

[209] Ross, S. A., and Elsohly, M. A., 1996, "The volatile oil composition of fresh and air-dried buds of Cannabis sativa," J. Nat. Prod.

[210] Mehmedic, Z., Chandra, S., Slade, D., Denham, H., Foster, S., Patel, A. S., Ross, S. A., Khan, I. A., and ElSohly, M. A., 2010, "Potency Trends of Δ9-THC and Other Cannabinoids in Confiscated Cannabis Preparations from 1993 to 2008*," Journal of Forensic Sciences, **55**(5), pp. 1209–1217.

[211] De Meijer, E., 2009, "Cannabis sativa plants rich in cannabichromene and its acid, extracts thereof and methods of obtaining extracts therefrom," (12/936,947).

[212] de Meijer, E., 2014, "The Chemical Phenotypes (Chemotypes) of Cannabis," Handbook of Cannabis, Oxford University Press, pp. 89–110.

[213] Clarke, R., and Merlin, M., 2013, Cannabis, Univ of California Press.

[214] Upton, R., Craker, L., ElSohly, M., Russo, E., Roman, A., Sexton, M., Marcu, J., and Swisher, D., 2013, "Cannabis Inflorescence," The American Herbal Pharmacoepia, p. 61.

[215] Ashton, C. H., 2001, "Pharmacology and effects of cannabis: a brief review.," The British Journal of Psychiatry, **178**, pp. 101–106.

[216] Harvey, D. J., 1999, "Absorption, Distribution, and Biotransformation of the Cannabinoids," Marihuana and Medicine, G.G. Nahas, K.M. Sutin, D. Harvey, S. Agurell, N. Pace, and R. Cancro, eds., Humana Press, Totowa, NJ, pp. 91–103.

[217] Harvey, D. J., 1992, "Cannabinoids," Mass Spectrometry, Springer US, Boston, MA, pp. 207–257.

[218] Harvey, D. J., 1985, "Identification of hepatic metabolites of n-heptyl-delta-1-tetrahydrocannabinol in the mouse.," Xenobiotica, **15**(3), pp. 187–197.

[219] Harvey, D. J., 1984, Chemistry, metabolism and pharmacokinetics of the cannabinoids, Raven Press. New York.

[220] Hawksworth, G., and McArdle, K., 2004, "Metabolism and pharmacokinetics of cannabinoids," The Medicinal Uses of Cannabis and Cannabinoids, G. Guy, B.A. Whittle, and P.J. Robson, eds., Pharmaceutical Press, pp. 206–228.

[221] NAKAZAWA, K., and COSTA, E., 1971, "Metabolism of Δ9-Tetrahydrocannabinol by Lung and Liver Homogenates of Rats treated with Methylcholanthrene," Nature, **234**(5323), pp. 48–49.

[222] WIDMAN, M., NORDQVIST, M., DOLLERY, C. T., and BRIANT, R. H., 2011, "Metabolism of Δ1-tetrahydrocannabinol by the isolated perfused dog lung. Comparison with in vitro liver metabolism," Journal of Pharmacy and Pharmacology, **27**(11), pp. 842–848.

[223] Harvey, D. J., and Paton, W. D. M., 1976, "Examination of the Metabolites of Δ1-Tetrahydrocannabinol in Mouse Liver, Heart, and Lung by Combined Gas Chromatography and Mass Spectrometry," Marihuana, Springer Berlin Heidelberg, Berlin, Heidelberg, pp. 93–109.

[224] Leighty, E. G., 1973, "Metabolism and distribution of cannabinoids in rats after different methods of administration," Biochemical Pharmacology, **22**(13), pp. 1613–1621.

[225] Schwope, D. M., Karschner, E. L., Gorelick, D. A., and Huestis, M. A., 2011, "Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration.," Clinical Chemistry, **57**(10), pp. 1406–1414.

[226] Schwope, D. M., Scheidweiler, K. B., and Huestis, M. A., 2011, "Direct quantification of cannabinoids and cannabinoid glucuronides in whole blood by liquid chromatography–tandem mass spectrometry," Anal Bioanal Chem, **401**(4), pp. 1273–1283.

[227] Skopp, G., and Potsch, L., 2004, "An Investigation of the Stability of Free and Glucuronidated 11-Nor- 9-Tetrahydrocannabinol-9-carboxylic Acid in Authentic Urine Samples," J Anal Toxicol, **28**(1), pp. 35–40.

[228] Huestis, M. A., Henningfield, J. E., and Cone, E. J., 1992, "Blood cannabinoids. I. Absorption of THC and formation of 11-OH-THC and THCCOOH during and after smoking marijuana.," J Anal Toxicol, **16**(5), pp. 276–282.

[229] Brenneisen, R., Egli, A., Elsohly, M. A., Henn, V., and Spiess, Y., 1996, "The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients.," Int J Clin Pharmacol Ther, **34**(10), pp. 446–452.

[230] Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., and Perez-Reyes, M., 1983, "Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women," Clin Pharmacol Ther, **34**(3), pp. 352–363.

[231] Reuter, S. E., and Martin, J. H., 2016, "Pharmacokinetics of Cannabis in Cancer Cachexia-Anorexia Syndrome.," Clin Pharmacokinet, pp. 1–6.

[232] Frytak, S., Moertel, C. G., and Rubin, J., 1984, "Metabolic studies of delta-9-tetrahydrocannabinol in

cancer patients.," Cancer Treat Rep, **68**(12), pp. 1427–1431.

[233] Wall, M. E., Sadler, B. M., Brine, D., Taylor, H., and Perez-Reyes, M., 1983, "Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women," Clin Pharmacol Ther, **34**(3), pp. 352–363.

[234] TIMPONE, J. G., WRIGHT, D. J., Li, N., EGORIN, M. J., ENAMA, M. E., MAYERS, J., and GALETTO, G., 1997, "The Safety and Pharmacokinetics of Single-Agent and Combination Therapy with Megestrol Acetate and Dronabinol for the Treatment of HIV Wasting Syndrome," AIDS Research and Human Retroviruses, **13**(4), pp. 305–315.

[235] Agurell, S., Halldin, M., Lindgren, J. E., Ohlsson, A., Widman, M., Gillespie, H., and Hollister, L., 1986, "Pharmacokinetics and metabolism of delta 1-tetrahydrocannabinol and other cannabinoids with emphasis on man.," Pharmacological Reviews, **38**(1), pp. 21–43.

[236] Ohlsson, A., Lindgren, J. E., Andersson, S., Agurell, S., Gillespie, H., and Hollister, L. E., 1986, "Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration.," Biomed. Environ. Mass Spectrom., **13**(2), pp. 77–83.

[237] Wall, M. E., Brine, D. R., Pitt, C. G., and Perez-Reyes, M., 1972, "Identification of 9 -tetrahydrocannabinol and metabolites in man.," J. Am. Chem. Soc., **94**(24), pp. 8579–8581.

[238] Wall, M. E., 1975, "Recent Advances in the Chemistry and Metabolism of the Cannabinoids," Recent Advances in Phytochemistry, Springer US, Boston, MA, pp. 29–61.

[239] Wall, M. E., and Perez-Reyes, M., 1981, "The metabolism of delta 9-tetrahydrocannabinol and related cannabinoids in man.," J Clin Pharmacol, **21**(8-9 Suppl), pp. 178S–189S.

[240] Harvey, D. J., 1999, "Absorption, Distribution, and Biotransformation of the Cannabinoids," Marihuana and Medicine, G.G. Nahas, K.M. Sutin, D. Harvey, S. Agurell, N. Pace, and R. Cancro, eds., Humana Press, Totowa, NJ, pp. 91–103.

[241] Huestis, M. A., and Smith, M. L., 2014, "Cannabinoid Pharmacokinetics and Disposition in Alternative Matrices," Handbook of Cannabis, Oxford University Press, pp. 296–316.

[242] Huestis, M. A., 2005, "Pharmacokinetics and Metabolism of the Plant Cannabinoids, Δ 9-Tetrahydrocannibinol, Cannabidiol and Cannabinol," Cannabinoids, **168**(Chapter 23), pp. 657–690.

[243] Lindgren, J.-E., Ohlsson, A., Agurell, S., Hollister, L., and Gillespie, H., 1981, "Clinical effects and plasma levels of Δ9-Tetrahydrocannabinol (Δ9-THC) in heavy and light users of cannabis," Psychopharmacology, **74**(3), pp. 208–212.

[244] Ohlsson, A., Lindgren, J.-E., Wahlén, A., Agurell, S., Hollister, L. E., and Gillespie, H. K., 1982, "Single dose kinetics of deuterium labelled Δ1-tetrahydrocannabinol in heavy and light cannabis users," Biological Mass Spectrometry, **9**(1), pp. 6–10.

[245] Pomahacova, B., Van der Kooy, F., and Verpoorte, R., 2009, "Cannabis smoke condensate III: The cannabinoid content of vaporised Cannabis sativa," Inhalation Toxicology, **00**(00), pp. 090619130156077–5.

[246] Van der Kooy, F., Pomahacova, B., and Verpoorte, R., 2008, "Cannabis smoke condensate I: the effect of

different preparation methods on tetrahydrocannabinol levels.," Inhalation Toxicology, **20**(9), pp. 801–804.

[247] Van der Kooy, F., Pomahacova, B., and Verpoorte, R., 2009, "Cannabis Smoke Condensate II: Influence of Tobacco on Tetrahydrocannabinol Levels," Inhalation Toxicology, **21**(2), pp. 87–90.

[248] Huestis, M. A., and Smith, M. L., 2014, "Cannabinoid pharmacokinetics and disposition in alternative matrices," Handbook of Cannabis.

[249] Karschner, E. L., Schwilke, E. W., Lowe, R. H., Darwin, W. D., Pope, H. G., Herning, R., Cadet, J. L., and Huestis, M. A., 2009, "Do ΔΔ 9-tetrahydrocannabinol concentrations indicate recent use in chronic cannabis users?," Addiction, **104**(12), pp. 2041–2048.

[250] Schwilke, E. W., Schwope, D. M., Karschner, E. L., Lowe, R. H., Darwin, W. D., Kelly, D. L., Goodwin, R. S., Gorelick, D. A., and Huestis, M. A., 2009, "Delta9-tetrahydrocannabinol (THC), 11-hydroxy-THC, and 11-nor-9-carboxy-THC plasma pharmacokinetics during and after continuous high-dose oral THC.," Clinical Chemistry, **55**(12), pp. 2180–2189.

[251] Hollister, L. E., GILLESPIE, H. K., Ohlsson, A., Lindgren, J. E., WAHLEN, A., and Agurell, S., 2013, "Do Plasma Concentrations of Δ 9-Tetrahydrocannabinol Reflect the Degree of Intoxication?," The Journal of Clinical Pharmacology, **21**(S1), pp. 171S–177S.

[252] Ohlsson, A., Lindgren, J. E., WAHLEN, A., Agurell, S., Hollister, L. E., and GILLESPIE, H. K., 1980, "Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking," Clin Pharmacol Ther, **28**(3), pp. 409–416.

[253] Law, B., Mason, P. A., Moffat, A. C., Gleadle, R. I., and King, L. J., 1984, "Forensic aspects of the metabolism and excretion of cannabinoids following oral ingestion of cannabis resin," Journal of Pharmacy and Pharmacology, **36**(5), pp. 289–294.

[254] Chiang, C. W., Barnett, G., and Brine, D., 1983, "Systemic absorption of delta 9-tetrahydrocannabinol after ophthalmic administration to the rabbit.," J Pharm Sci, **72**(2), pp. 136–138.

[255] Touitou, E., and Fabin, B., 1988, "Altered skin permeation of a highly lipophilic molecule: tetrahydrocannabinol," International Journal of Pharmaceutics, **43**(1-2), pp. 17–22.

[256] Touitou, E., Fabin, B., Dany, S., and Almog, S., 1988, "Transdermal delivery of tetrahydrocannabinol," International Journal of Pharmaceutics, **43**(1-2), pp. 9–15.

[257] Colbert, M., 2016, "With Cannabis Research Blocked In America, Americans for Safe Access Goes to Prague," httptheleafonline.comcbusinesscannabis-research-blocked-america-americans-safe-access-goes-prague.

[258] Machado Rocha, F. C., Stefano, S. C., De Cassia Haike, R., Rosa Oliveiria, L. M. Q., and Da Silveira, D. X., 2008, "Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis.," Eur J Cancer Care (Engl), **17**(5), pp. 431–443.

[259] Institute of Medicine, 1999, Marijuana and Medicine:, National Academies Press.

[260] Eddy, M., 2010, Medical Marijuana: Review and Analysis of Federal and State Policies. Congressional Research Service.

[261] Musty, R. E., and Rossi, R., 2001, "Effects of Smoked Cannabis and Oral δ 9-Tetrahydrocannabinol on Nausea and Emesis After Cancer Chemotherapy," Journal of Cannabis therapeutics, **1**(1), pp. 29–56.

[262] Guzmán, M., 2003, "Cannabinoids: potential anticancer agents," Nature Reviews Cancer, **3**(10), pp. 745–755.

[263] Gieringer, D., 1996, Review of the Human Studies on the Medical Use of Marijuana. norml. org/medical/medmj. studies. shtml, See state studies at www. drugpolicy. org.

[264] Committee, S. A. T. S., 1998, Cannabis: the scientific and medical evidence, House of Commons Library Research ….

[265] Association, B. M., 1997, Therapeutic Uses of Cannabis, CRC Press.

[266] Todaro, B., 2012, "Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting.," J Natl Compr Canc Netw, **10**(4), pp. 487–492.

[267] Nikan, M., Nabavi, S. M., and Manayi, A., 2016, "Ligands for cannabinoid receptors, promising anticancer agents.," Life Sciences, **146**, pp. 124–130.

[268] Rocha, F. C. M., Santos Júnior, Dos, J. G., Stefano, S. C., and da Silveira, D. X., 2014, "Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas.," J Neurooncol, **116**(1), pp. 11–24.

[269] Sarfaraz, S., Afaq, F., Adhami, V. M., and Mukhtar, H., 2005, "Cannabinoid receptor as a novel target for the treatment of prostate cancer.," Cancer Res, **65**(5), pp. 1635–1641.

[270] Ruiz, L., Miguel, A., and Díaz-Laviada, I., 1999, "Δ 9-Tetrahydrocannabinol induces apoptosis in human prostate PC-3 cells via a receptor-independent mechanism," FEBS Letters, **458**(3), pp. 400–404.

[271] Patsos, H. A., Hicks, D. J., Dobson, R. R. H., Greenhough, A., Woodman, N., Lane, J. D., Williams, A. C., and Paraskeva, C., 2005, "The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase 2.," Gut, **54**(12), pp. 1741–1750.

[272] Casanova, M. L., Blázquez, C., Martínez-Palacio, J., Villanueva, C., Fernández-Aceñero, M. J., Huffman, J. W., Jorcano, J. L., and Guzmán, M., 2003, "Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors," J. Clin. Invest., **111**(1), pp. 43–50.

[273] Powles, T., Poele, te, R., Shamash, J., Chaplin, T., Propper, D., Joel, S., Oliver, T., and Liu, W. M., 2005, "Cannabis-induced cytotoxicity in leukemic cell lines: the role of the cannabinoid receptors and the MAPK pathway," Blood, **105**(3), pp. 1214–1221.

[274] Jia, W., Hegde, V. L., Singh, N. P., Sisco, D., Grant, S., Nagarkatti, M., and Nagarkatti, P. S., 2006, "Delta9-tetrahydrocannabinol-induced apoptosis in Jurkat leukemia T cells is regulated by translocation of Bad to mitochondria.," Mol Cancer Res, **4**(8), pp. 549–562.

[275] Preet, A., Ganju, R. K., and Groopman, J. E., 2008, "|[Delta]|9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo," Oncogene, **27**(3), pp. 339–346.

[276] Baek, S., Kim, Y. O., Kwag, J. S., Choi, K. E., Jung, W. Y., and Han, D. S., 1998, Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells, Archives of Pharmacal ….

[277] Carracedo, A., Gironella, M., Lorente, M., Garcia, S., Guzmán, M., Velasco, G., and Iovanna, J. L., 2006, "Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes.," Cancer Res, **66**(13), pp. 6748–6755.

[278] Michalski, C. W., Oti, F. E., Erkan, M., Sauliunaite, D., Bergmann, F., Pacher, P., Bátkai, S., Müller, M. W., Giese, N. A., Friess, H., and Kleeff, J., 2008, "Cannabinoids in pancreatic cancer: correlation with survival and pain.," Int. J. Cancer, **122**(4), pp. 742–750.

[279] Ramer, R., and Hinz, B., 2008, "Inhibition of cancer cell invasion by cannabinoids via increased expression of tissue inhibitor of matrix metalloproteinases-1.," J. Natl. Cancer Inst., **100**(1), pp. 59–69.

[280] Whyte, D. A., Al-Hammadi, S., Balhaj, G., Brown, O. M., Penefsky, H. S., and Souid, A.-K., 2010, "Cannabinoids inhibit cellular respiration of human oral cancer cells.," Pharmacology, **85**(6), pp. 328–335.

[281] Leelawat, S., Leelawat, K., Narong, S., and Matangkasombut, O., 2010, "The dual effects of delta(9)-tetrahydrocannabinol on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration.," Cancer Invest., **28**(4), pp. 357–363.

[282] Sánchez, C., Galve-Roperh, I., Canova, C., Brachet, P., and Guzman, M., 1998, "Delta9-tetrahydrocannabinol induces apoptosis in C6 glioma cells.," FEBS Letters, **436**(1), pp. 6–10.

[283] Gustafsson, K., Christensson, B., Sander, B., and Flygare, J., 2006, "Cannabinoid receptor-mediated apoptosis induced by R(+)-methanandamide and Win55,212-2 is associated with ceramide accumulation and p38 activation in mantle cell lymphoma.," Molecular Pharmacology, **70**(5), pp. 1612–1620.

[284] Gustafsson, K., Wang, X., Severa, D., Eriksson, M., Kimby, E., Merup, M., Christensson, B., Flygare, J., and Sander, B., 2008, "Expression of cannabinoid receptors type 1 and type 2 in non-Hodgkin lymphoma: Growth inhibition by receptor activation," Int. J. Cancer, **123**(5), pp. 1025–1033.

[285] Galve-Roperh, I., Sánchez, C., Cortés, M. L., Gómez del Pulgar, T., Izquierdo, M., and Guzman, M., 2000, "Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation.," Nat. Med., **6**(3), pp. 313–319.

[286] Blázquez, C., Casanova, M. L., Planas, A., Gómez del Pulgar, T., Villanueva, C., Fernández-Aceñero, M. J., Aragonés, J., Huffman, J. W., Jorcano, J. L., and Guzmán, M., 2003, "Inhibition of tumor angiogenesis by cannabinoids.," The FASEB Journal, **17**(3), pp. 529–531.

[287] Alexander, A., Smith, P. F., and Rosengren, R. J., 2009, "Cannabinoids in the treatment of cancer," CANCER LETTERS, pp. 1–7.

[288] Olea-Herrero, N., Vara, D., Malagarie-Cazenave, S., and Díaz-Laviada, I., 2009, "Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: Involvement of CB2," Br J Cancer, **101**(6), pp. 940–950.

[289] Sánchez, C., de Ceballos, M. L., Gómez del Pulgar, T., Rueda, D., Corbacho, C., Velasco, G., Galve-Roperh, I., Huffman, J. W., Ramón y Cajal, S., and Guzman, M., 2001, "Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor.," Cancer Res, **61**(15), pp. 5784–5789.

[290] Liu, W. M., Scott, K. A., Shamash, J., Joel, S., and Powles, T. B., 2015, "Enhancing the in vitrocytotoxic

activity of Δ 9-tetrahydrocannabinol in leukemic cells through a combinatorial approach," Leukemia & Lymphoma, **49**(9), pp. 1800–1809.

[291] Torres, S., Lorente, M., Rodriguez-Fornes, F., Hernandez-Tiedra, S., Salazar, M., Garcia-Taboada, E., Barcia, J., Guzman, M., and Velasco, G., 2011, "A Combined Preclinical Therapy of Cannabinoids and Temozolomide against Glioma," Mol. Cancer Ther., **10**(1), pp. 90–103.

[292] González, S., Mauriello-Romanazzi, G., Berrendero, F., Ramos, J. A., Franzoni, M. F., and Fernández-Ruiz, J., 2000, "Decreased cannabinoid CB1 receptor mRNA levels and immunoreactivity in pituitary hyperplasia induced by prolonged exposure to estrogens.," Pituitary, **3**(4), pp. 221–226.

[293] Pagotto, U., Marsicano, G., Fezza, F., Theodoropoulou, M., Grübler, Y., Stalla, J., Arzberger, T., Milone, A., Losa, M., Di Marzo, V., Lutz, B., and Stalla, G. K., 2001, "Normal human pituitary gland and pituitary adenomas express cannabinoid receptor type 1 and synthesize endogenous cannabinoids: first evidence for a direct role of cannabinoids on hormone modulation at the human pituitary level.," The Journal of Clinical Endocrinology & Metabolism, **86**(6), pp. 2687–2696.

[294] McAllister, S. D., Soroceanu, L., and Desprez, P.-Y., 2015, "The Antitumor Activity of Plant-Derived Non-Psychoactive Cannabinoids.," J Neuroimmune Pharmacol, **10**(2), pp. 1–13.

[295] Ramer, R., and Hinz, B., 2010, "Cyclooxygenase-2 and tissue inhibitor of matrix metalloproteinases-1 confer the antimigratory effect of cannabinoids on human trabecular meshwork cells," Biochemical Pharmacology, **80**(6), pp. 846–857.

[296] Ligresti, A., Moriello, A. S., Starowicz, K., Matias, I., Pisanti, S., De Petrocellis, L., Laezza, C., Portella, G., Bifulco, M., and Di Marzo, V., 2006, "Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma.," Journal of Pharmacology and Experimental Therapeutics, **318**(3), pp. 1375–1387.

[297] Caffarel, M. M., Andradas, C., Mira, E., Pérez-Gómez, E., Cerutti, C., Moreno-Bueno, G., Flores, J. M., García-Real, I., Palacios, J., Mañes, S., Guzmán, M., and Sánchez, C., 2010, "Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition," Molecular Cancer, **9**(1), p. 196.

[298] De Petrocellis, L., Melck, D., Palmisano, A., Bisogno, T., Laezza, C., Bifulco, M., and Di Marzo, V., 1998, "The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation.," Proc. Natl. Acad. Sci. U.S.A., **95**(14), pp. 8375–8380.

[299] McAllister, S. D., Christian, R. T., Horowitz, M. P., Garcia, A., and Desprez, P. Y., 2007, "Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells," Mol. Cancer Ther., **6**(11), pp. 2921–2927.

[300] Blázquez, C., 2004, "Cannabinoids Inhibit the Vascular Endothelial Growth Factor Pathway in Gliomas," Cancer Res, **64**(16), pp. 5617–5623.

[301] Marcu, J. P., Christian, R. T., Lau, D., Zielinski, A. J., Horowitz, M. P., Lee, J., Pakdel, A., Allison, J., Limbad, C., Moore, D. H., Yount, G. L., Desprez, P.-Y., and McAllister, S. D., 2010, "Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival.," Mol. Cancer Ther., **9**(1), pp. 180–189.

[302] Scott, K. A., Dalgleish, A. G., and Liu, W. M., 2014, "The Combination of Cannabidiol and Δ9-Tetrahydrocannabinol Enhances the Anticancer Effects of Radiation in an Orthotopic Murine Glioma

Model.," Mol. Cancer Ther.

[303] Cridge, B. J., and Rosengren, R. J., 2013, "Critical appraisal of the potential use of cannabinoids in cancer management.," Cancer Manag Res, **5**, pp. 301–313.

[304] Stella, N., 2010, "Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas," Glia, **58**(9), pp. 1017–1030.

[305] Guzman, M., Duarte, M. J., Blázquez, C., Ravina, J., Rosa, M. C., Galve-Roperh, I., Sánchez, C., Velasco, G., and González-Feria, L., 2006, "A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme," Br J Cancer, **95**(2), pp. 197–203.

[306] Parolaro, D., and Massi, P., 2008, "Cannabinoids as potential new therapy for the treatment of gliomas," Expert Rev Neurother, **8**(1), pp. 37–49.

[307] Javid, F. A., Phillips, R. M., Afshinjavid, S., Verde, R., and Ligresti, A., 2016, "Cannabinoid pharmacology in cancer research_ A new hope for cancer patients?," European Journal of Pharmacology, **775**(c), pp. 1–14.

[308] Liang, C., McClean, M. D., Marsit, C., Christensen, B., Peters, E., Nelson, H. H., and Kelsey, K. T., 2009, "A population-based case-control study of marijuana use and head and neck squamous cell carcinoma.," Cancer Prev Res (Phila), **2**(8), pp. 759–768.

[309] Foroughi, M., Hendson, G., Sargent, M. A., and Steinbok, P., 2011, "Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas—possible role of Cannabis inhalation," Childs Nerv Syst, **27**(4), pp. 671–679.

[310] Prentiss, D., Power, R., Balmas, G., Tzuang, G., and Israelski, D. M., 2004, "Patterns of Marijuana Use Among Patients With HIV/AIDS Followed in a Public Health Care Setting," J. Acquir. Immune Defic. Syndr., **35**(1), pp. 38–45.

[311] Corless, I. B., Lindgren, T., Holzemer, W., Robinson, L., Moezzi, S., Kirksey, K., Coleman, C., Tsai, Y. F., Sanzero Eller, L., Hamilton, M. J., Sefcik, E. F., Canaval, G. E., Rivero Mendez, M., Kemppainen, J. K., Bunch, E. H., Nicholas, P. K., Nokes, K. M., Dole, P., and Reynolds, N., 2009, "Marijuana Effectiveness as an HIV Self-Care Strategy," Clinical Nursing Research, **18**(2), pp. 172–193.

[312] de Jong, B. C., Prentiss, D., McFarland, W., Machekano, R., and Israelski, D. M., 2005, "Marijuana Use and Its Association With Adherence to Antiretroviral Therapy Among HIV-Infected Persons With Moderate to Severe Nausea," J. Acquir. Immune Defic. Syndr., **38**(1), pp. 43–46.

[313] Hollister, L. E., 2016, "Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine," Clin Pharmacol Ther, **12**(1), pp. 44–49.

[314] Foltin, R. W., Fischman, M. W., and Byrne, M. F., 1988, "Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory," Appetite, **11**(1), pp. 1–14.

[315] Raborn, E. S., Jamerson, M., Marciano-Cabral, F., and Cabral, G. A., 2014, "Cannabinoid inhibits HIV-1 Tat-stimulated adhesion of human monocyte-like cells to extracellular matrix proteins.," Life Sciences, **104**(1-2), pp. 15–23.

[316] Costantino, C. M., Gupta, A., Yewdall, A. W., Dale, B. M., Devi, L. A., and Chen, B. K., 2012, "Cannabinoid

receptor 2-mediated attenuation of CXCR4-tropic HIV infection in primary CD4+ T cells.," PLoS ONE, **7**(3), p. e33961.

[317] Russo, E. B., 2012, Cannabis Therapeutics in HIV/AIDS, Routledge.

[318] Rahn, E. J., and Hohmann, A. G., 2009, "Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside.," Neurotherapeutics, **6**(4), pp. 713–737.

[319] Ellis, R. J., Toperoff, W., Vaida, F., van den Brande, G., Gonzales, J., Gouaux, B., Bentley, H., and Atkinson, J. H., 2009, "Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial.," Neuropsychopharmacology, **34**(3), pp. 672–680.

[320] Karst, M., Salim, K., Burstein, S., Conrad, I., Hoy, L., and Schneider, U., 2003, "Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial.," JAMA, **290**(13), pp. 1757–1762.

[321] Abrams, D. I., Jay, C. A., Shade, S. B., Vizoso, H., Reda, H., Press, S., Kelly, M. E., Rowbotham, M. C., and Petersen, K. L., 2007, "Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial.," Neurology, **68**(7), pp. 515–521.

[322] Bachhuber, M. A., Saloner, B., Cunningham, C. O., and Barry, C. L., 2014, "Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010.," JAMA Intern Med, **174**(10), pp. 1668–1673.

[323] Ellis, R. J., Toperoff, W., Vaida, F., van den Brande, G., Gonzales, J., Gouaux, B., Bentley, H., and Atkinson, J. H., 2008, "Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial," Neuropsychopharmacology, **34**(3), pp. 672–680.

[324] Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., and Fishman, S., 2008, "A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain.," J Pain, **9**(6), pp. 506–521.

[325] Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., Gamsa, A., Bennett, G. J., and Collet, J.-P., 2010, "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial.," CMAJ, **182**(14), pp. E694–701.

[326] Rog, D. J., Nurmikko, T. J., Friede, T., and Young, C. A., 2005, "Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis.," Neurology, **65**(6), pp. 812–819.

[327] Nurmikko, T. J., Serpell, M. G., Hoggart, B., Toomey, P. J., Morlion, B. J., and Haines, D., 2007, "Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial," PAIN, **133**(1), pp. 210–220.

[328] Desroches, J., and Beaulieu, P., 2010, "Opioids and cannabinoids interactions: involvement in pain management.," Curr Drug Targets, **11**(4), pp. 462–473.

[329] Welch, S. P., and Eads, M., 1999, "Synergistic interactions of endogenous opioids and cannabinoid systems.," Brain Research, **848**(1-2), pp. 183–190.

[330] Wallace, M., Schulteis, G., Atkinson, J. H., WOLFSON, T., Lazzaretto, D., Bentley, H., Gouaux, B., and Abramson, I., 2007, "Dose-dependent effects of smoked cannabis on capsaicin-induced pain and

hyperalgesia in healthy volunteers.," Anesthesiology, **107**(5), pp. 785–796.

[331] Lucas, P., 2012, "Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain.," Journal of Psychoactive Drugs, **44**(2), pp. 125–133.

[332] Abrams, D. I., Couey, P., Shade, S. B., Kelly, M. E., and Benowitz, N. L., 2011, "Cannabinoid–Opioid Interaction in Chronic Pain," Clin Pharmacol Ther, **90**(6), pp. 844–851.

[333] Morel, L. J., Giros, B., and eacute, V. E. R. D., 2009, "Adolescent Exposure to Chronic Delta-9-Tetrahydrocannabinol Blocks Opiate Dependence in Maternally Deprived Rats," pp. 1–8.

[334] Reiman, A., 2009, "Cannabis as a substitute for alcohol and other drugs.," Harm Reduct J, **6**, pp. 35–35.

[335] Attar, B. M., and Van Thiel, D. H., 2016, "Hepatitis C virus: A time for decisions. Who should be treated and when?," World J Gastrointest Pharmacol Ther, **7**(1), pp. 33–40.

[336] Sylvestre, D. L., Clements, B. J., and Malibu, Y., 2006, "Cannabis use improves retention and virological outcomes in patients treated for hepatitis C.," Eur J Gastroenterol Hepatol, **18**(10), pp. 1057–1063.

[337] O'Shaughnessy, W. B., 1843, "On the Preparations of the Indian Hemp, or Gunjah," Prov Med Surg J, **s1-5**(123), pp. 363–369.

[338] Russo, E., 2013, "The Role of Cannabis and Cannabinoids in Pain Management," Weiner's Pain Management, CRC Press, pp. 823–844.

[339] Hazekamp, A., and Grotenhermen, F., 2010, "Review on clinical studies with cannabis and cannabinoids 2005-2009," Cannabinoids, **5**(special), pp. 1–21.

[340] Andreae, M. H., Carter, G. M., Shaparin, N., Suslov, K., Ellis, R. J., Ware, M. A., Abrams, D. I., Prasad, H., Wilsey, B., Indyk, D., Johnson, M., and Sacks, H. S., 2015, "Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data.," J Pain, **16**(12), pp. 1221–1232.

[341] Carter, G. T., Javaher, S. P., Nguyen, M. H., Garret, S., and Carlini, B. H., 2015, "Re-branding cannabis: the next generation of chronic pain medicine?," Pain Management, **5**(1), pp. 13–21.

[342] Pillarisetti, S., Alexander, C. W., and Khanna, I., 2009, "Pain and beyond: fatty acid amides and fatty acid amide hydrolase inhibitors in cardiovascular and metabolic diseases," Drug Discovery Today, **14**(23-24), pp. 1098–1111.

[343] Richardson, J. D., Kilo, S., and Hargreaves, K. M., 1998, "Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors," PAIN, **75**(1), pp. 111–119.

[344] Cichewicz, D. L., and McCarthy, E. A., 2003, "Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration.," Journal of Pharmacology and Experimental Therapeutics, **304**(3), pp. 1010–1015.

[345] Cox, M. L., Haller, V. L., and Welch, S. P., 2007, "Synergy between delta9-tetrahydrocannabinol and morphine in the arthritic rat.," European Journal of Pharmacology, **567**(1-2), pp. 125–130.

[346] Cichewicz, D. L., 2004, "Synergistic interactions between cannabinoid and opioid analgesics.," Life Sciences, **74**(11), pp. 1317–1324.

[347] Smith, P. A., Selley, D. E., Sim-Selley, L. J., and Welch, S. P., 2007, "Low dose combination of morphine and Δ9-tetrahydrocannabinol circumvents antinociceptive tolerance and apparent desensitization of receptors," European Journal of Pharmacology, **571**(2-3), pp. 129–137.

[348] Meng, I. D., Manning, B. H., Martin, W. J., and Fields, H. L., 1998, "An analgesia circuit activated by cannabinoids.," Nature, **395**(6700), pp. 381–383.

[349] Klarreich, E., 2001, "Cannabis spray blunts pain," news@nature.

[350] Holdcroft, A., Smith, M., Jacklin, A., Hodgson, H., Smith, B., Newton, M., and Evans, F., 1997, "Pain relief with oral cannabinoids in familial Mediterranean fever," Anaesthesia, **52**(5), pp. 483–486.

[351] Leslie L. Iversen Professor of Pharmacology University of Oxford, 2007, The Science of Marijuana, Oxford University Press, USA.

[352] Noyes, R., and Baram, D. A., 1974, "Cannabis analgesia.," Compr Psychiatry, **15**(6), pp. 531–535.

[353] Randall, R. C., and Administration, U. S. D. E., 1989, Marijuana, medicine & the law, Galen Pr.

[354] Rog, D. J., 2010, "Cannabis-based medicines in multiple sclerosis – A review of clinical studies," Immunobiology, **215**(8), pp. 658–672.

[355] Johnson, J. R., Burnell-Nugent, M., Lossignol, D., Ganae-Motan, E. D., Potts, R., and Fallon, M. T., 2010, "Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain.," Journal of Pain and Symptom Management, **39**(2), pp. 167–179.

[356] GW Pharma Ltd., 2010, "Phase IIb Cancer Pain Trial Data."

[357] Kinsey, S. G., Long, J. Z., Cravatt, B. F., and Lichtman, A. H., 2010, "Inhibiting endocannabinoid catabolic enzymes attenuates neuropathic pain via distinct cannabinoid receptor mediated mechanisms of action," Brain, Behavior, and Immunity, **24**, p. S6.

[358] Guindon, J., and Hohmann, A. G., 2008, "Cannabinoid CB 2receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain," British Journal of Pharmacology, **153**(2), pp. 319–334.

[359] Baker, D., Pryce, G., Croxford, J. L., Brown, P., Pertwee, R. G., Huffman, J. W., and Layward, L., 2000, "Cannabinoids control spasticity and tremor in a multiple sclerosis model," Nature, **404**(6773), pp. 84–87.

[360] Petro, D. J., 1980, Marihuana as a therapeutic agent for muscle spasm or spasticity, Psychosomatics.

[361] Petro, D. J., 2002, "Cannabis in Multiple Sclerosis: Women's Health Concerns," Journal of Cannabis therapeutics, **2**(3-4), pp. 161–175.

[362] Russo, E. B., 2013, Cannabis and cannabinoids: pharmacology, toxicology, and therapeutic potential.

[363] Clifford, D. B., 1983, "Tetrahydrocannabinol for tremor in multiple sclerosis," Annals of Neurology, **13**(6), pp. 669–671.

[364] Meinck, H. M., Sch nle, P. W., and Conrad, B., 1989, "Effect of cannabinoids on spasticity and ataxia in

multiple sclerosis," Journal of Neurology, **236**(2), pp. 120–122.

[365] Achiron, A., Miron, S., Lavie, V., Margalit, R., and Biegon, A., 2000, "Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis," Journal of Neuroimmunology, **102**(1), pp. 26–31.

[366] Pryce, G., 2003, "Cannabinoids inhibit neurodegeneration in models of multiple sclerosis," Brain, **126**(10), pp. 2191–2202.

[367] Baker, D., Jackson, S. J., and Pryce, G., 2009, "Cannabinoid control of neuroinflammation related to multiple sclerosis," British Journal of Pharmacology, **152**(5), pp. 649–654.

[368] Zhang, M., Martin, B. R., Adler, M. W., Razdan, R. J., Kong, W., Ganea, D., and Tuma, R. F., 2009, "Modulation of Cannabinoid Receptor Activation as a Neuroprotective Strategy for EAE and Stroke," J Neuroimmune Pharmacol, **4**(2), pp. 249–259.

[369] Lakhan, S. E., and Rowland, M., 2009, "Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review," BMC Neurology, **9**(1), p. 59.

[370] Baker, D., and Pryce, G., 2008, "The Endocannabinoid System and Multiple Sclerosis," Curr. Pharm. Des., **14**(23), pp. 2326–2336.

[371] Jean-Gilles, L., Feng, S., Tench, C. R., Chapman, V., Kendall, D. A., Barrett, D. A., and Constantinescu, C. S., 2009, "Plasma endocannabinoid levels in multiple sclerosis.," Journal of the Neurological Sciences, **287**(1-2), pp. 212–215.

[372] Fernández, O., 2014, "Advances in the management of multiple sclerosis spasticity: recent clinical trials.," Eur. Neurol., **72 Suppl 1**(s1), pp. 9–11.

[373] Tyagi, P., Tyagi, V., Yoshimura, N., and Chancellor, M., 2010, "Functional role of cannabinoid receptors in urinary bladder.," Indian J Urol, **26**(1), pp. 26–35.

[374] Collin, C., Davies, P., Mutiboko, I. K., Ratcliffe, S., for the Sativex Spasticity in MS Study Group, 2007, "Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis," European Journal of Neurology, **14**(3), pp. 290–296.

[375] Zajicek, J., Fox, P., Sanders, H., Wright, D., Vickery, J., Nunn, A., Thompson, A., UK MS Research Group, 2003, "Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial.," Lancet, **362**(9395), pp. 1517–1526.

[376] Muller-Vahl, K. R., Kolbe, H., Schneider, U., and Emrich, H. M., 1999, "Cannabis in movement disorders.," Forsch Komplementarmed, **6 Suppl 3**, pp. 23–27.

[377] Amtmann, D., Weydt, P., Johnson, K. L., Jensen, M. P., and Carter, G. T., 2004, "Survey of cannabis use in patients with amyotrophic lateral sclerosis," American Journal of Hospice and Palliative Medicine, **21**(2), pp. 95–104.

[378] Lorenz, R., 2004, "On the application of cannabis in paediatrics and epileptology," Neuroendocrinology Letters.

[379] Malec, J., Harvey, R. F., and Cayner, J. J., 1982, "Cannabis effect on spasticity in spinal cord injury.," Arch Phys Med Rehabil, **63**(3), pp. 116–118.

[380] Dunn, M., and Davis, R., 1974, "The perceived effects of marijuana on spinal cord injured males.," Paraplegia, **12**(3), pp. 175–175.

[381] Hanigan, W. C., 1986, The Effects of Delta-9-THC on Human Spasticity, Journal of the American Society of Clinical ….

[382] Manno, J. E., Kiplinger, G. F., Haine, S. E., BENNETT, I. F., and Forney, R. B., 1970, "Comparative effects of smoking marihuana or placebo on human motor and mental performance.," Clin Pharmacol Ther, **11**(6), pp. 808–15.

[383] Howlett, A. C., 1995, "Pharmacology of Cannabinoid Receptors," Annu. Rev. Pharmacol. Toxicol., **35**(1), pp. 607–634.

[384] Abood, M. E., and Martin, B. R., 1996, "Molecular neurobiology of the cannabinoid receptor.," Int. Rev. Neurobiol., **39**, pp. 197–221.

[385] Maccarrone, M., Gasperi, V., and Catani, M. V., 2010, "The endocannabinoid system and its relevance for nutrition," Annual review of ….

[386] Hill, M. N., and Gorzalka, B. B., 2005, "Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression?," Behavioural Pharmacology, **16**(5-6), pp. 333–352.

[387] Di Marzo, V., and Wang, J., 2014, The Endocannabinoidome, Academic Press.

[388] Howlett, A. C., Reggio, P. H., Childers, S. R., Hampson, R. E., Ulloa, N. M., and Deutsch, D. G., 2011, "Endocannabinoid tone versus constitutive activity of cannabinoid receptors," British Journal of Pharmacology, **163**(7), pp. 1329–1343.

[389] Mechoulam, R., and Lichtman, A. H., 2003, Endocannabinoids. Stout guards of the central nervous system, Science. Oct.

[390] García-Arencibia, M., Garcia, C., and Fernández-Ruiz, J., 2009, "Cannabinoids and Parkinsons Disease," CNS Neurol Disord Drug Targets, **8**(6), pp. 432–439.

[391] Venderová, K., Růžička, E., Voříšek, V., and Višňovský, P., 2004, "Survey on cannabis use in Parkinson's disease: Subjective improvement of motor symptoms," Movement Disorders, **19**(9), pp. 1102–1106.

[392] Carroll, C. B., Bain, P. G., Teare, L., Liu, X., Joint, C., Wroath, C., Parkin, S. G., Fox, P., Wright, D., Hobart, J., and Zajicek, J. P., 2004, "Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study.," Neurology, **63**(7), pp. 1245–1250.

[393] Lago, E., and Fernández-Ruiz, J., 2007, "Cannabinoids and Neuroprotection in Motor-Related Disorders," CNS Neurol Disord Drug Targets, **6**(6), pp. 377–387.

[394] Frankel, J. P., Hughes, A., Lees, A. J., and Stern, G. M., 1990, "Marijuana for parkinsonian tremor.," Journal of Neurology, Neurosurgery & Psychiatry, **53**(5), pp. 436–436.

[395] Wade, D. T., Makela, P., Robson, P., House, H., and Bateman, C., 2004, "Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients.," Mult. Scler., **10**(4), pp. 434–441.

[396] Chagas, M. H. N., Zuardi, A. W., Tumas, V., Pena-Pereira, M. A., Sobreira, E. T., Bergamaschi, M. M.,

Santos, Dos, A. C., Teixeira, A. L., Hallak, J. E., and Crippa, J. A. S., 2014, "Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial.," J. Psychopharmacol. (Oxford), **28**(11), pp. 1088–1098.

[397] Zuardi, A. W., Crippa, J. A. S., Hallak, J. E. C., Pinto, J. P., Chagas, M. H. N., Rodrigues, G. G. R., Dursun, S. M., and Tumas, V., 2009, "Cannabidiol for the treatment of psychosis in Parkinson's disease.," J. Psychopharmacol. (Oxford), **23**(8), pp. 979–983.

[398] Chagas, M. H. N., Eckeli, A. L., Zuardi, A. W., Pena-Pereira, M. A., Sobreira-Neto, M. A., Sobreira, E. T., Camilo, M. R., Bergamaschi, M. M., Schenck, C. H., Hallak, J. E. C., Tumas, V., and Crippa, J. A. S., 2014, "Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series," Journal of Clinical Pharmacy and Therapeutics, **39**(5), pp. 564–566.

[399] Lotan, I., Treves, T. A., Roditi, Y., and Djaldetti, R., 2014, "Cannabis (Medical Marijuana) Treatment for Motor and Non–Motor Symptoms of Parkinson Disease: An Open-Label Observational Study," Clinical Neuropharmacology, **37**(2), pp. 41–44.

[400] Zuardi, A. W., Hallak, J. E. C., and Crippa, J. A. S., 2011, "Interaction between cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC): influence of administration interval and dose ratio between the cannabinoids," Psychopharmacologia, **219**(1), pp. 247–249.

[401] Burstein, S., 2015, "Cannabidiol (CBD) and its analogs: a review of their effects on inflammation.," BIOORGANIC & MEDICINAL CHEMISTRY, **23**(7), pp. 1377–1385.

[402] Russo, E. B., 2007, "History of Cannabis and Its Preparations in Saga, Science, and Sobriquet," Chemistry & Biodiversity, **4**(8), pp. 1614–1648.

[403] Barrett, M. L., Gordon, D., and Evans, F. J., 1985, "Isolation from cannabis sativa L. of cannflavin—a novel inhibitor of prostaglandin production," Biochemical Pharmacology, **34**(11), pp. 2019–2024.

[404] Sofia, R. D., Nalepa, S. D., Harakel, J. J., and Vassar, A. B., 1973, Antiemetic and analgesic properties of delta-9-THC compared with three other drugs, Eur. J. Pharmacol.

[405] James, J. S., 1998, "Marijuana, inflammation, and CT-3 (DMH-11C): cannabis leads to new class of antiinflammatory drugs.," AIDS Treat News, (No 287), pp. 1–5.

[406] Mechoulam, R., Parker, L. A., and Gallily, R., 2002, "Cannabidiol: an overview of some pharmacological aspects," … of Clinical Pharmacology.

[407] Malfait, A. M., Gallily, R., Sumariwalla, P. F., Malik, A. S., Andreakos, E., Mechoulam, R., and Feldmann, M., 2000, "The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis.," Proc. Natl. Acad. Sci. U.S.A., **97**(17), pp. 9561–9566.

[408] Costa, B., Colleoni, M., Conti, S., Parolaro, D., Franke, C., Trovato, A. E., and Giagnoni, G., 2004, "Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw.," Naunyn-Schmied Arch Pharmacol, **369**(3), pp. 294–299.

[409] Campbell, V. A., and Gowran, A., 2009, "Alzheimer's disease; taking the edge off with cannabinoids?," British Journal of Pharmacology, **152**(5), pp. 655–662.

[410] Walther, S., Mahlberg, R., Eichmann, U., and Kunz, D., 2006, "Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia," Psychopharmacologia, **185**(4), pp. 524–528.

[411] Straus, S. E., 2000, "Immunoactive cannabinoids: therapeutic prospects for marijuana constituents.," Proc. Natl. Acad. Sci. U.S.A., **97**(17), pp. 9363–9364.

[412] Volicer, L., Stelly, M., Morris, J., McLaughlin, J., and Volicer, B. J., 1997, "Effects of Dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease," International Journal of Geriatric Psychiatry, **12**(9), pp. 913–919.

[413] Eubanks, L. M., Rogers, C. J., Beuscher, Koob, G. F., Olson, A. J., Dickerson, T. J., and Janda, K. D., 2006, "A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology," Mol. Pharmaceutics, **3**(6), pp. 773–777.

[414] Ramírez, B. G., Blázquez, C., Gómez del Pulgar, T., Guzmán, M., and de Ceballos, M. L., 2005, "Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation.," Journal of Neuroscience, **25**(8), pp. 1904–1913.

[415] Marchalant, Y., Brothers, H. M., Norman, G. J., Karelina, K., DeVries, A. C., and Wenk, G. L., 2009, "Cannabinoids attenuate the effects of aging upon neuroinflammation and neurogenesis," Neurobiology of Disease, **34**(2), pp. 300–307.

[416] Julian, H. L., 2008, Israeli Research Shows Cannabidiol May Slow Alzheimer's Disease, Israel National News.

[417] Whalley, B. J., 2014, "Cannabis In the Managment and Treatment of Seizure and Epilepsy: A Scientific Review.," The American Herbal Pharmacoepia, pp. 1–33.

[418] Davis, J. P., and Ramsey, H. H., 1949, "Antiepileptic action of marihuana-active substances," Federation Proceedings.

[419] Consroe, P. F., Wood, G. C., and Buchsbaum, H., 1975, "Anticonvulsant nature of marihuana smoking.," JAMA, **234**(3), pp. 306–307.

[420] Mortati, K., Dworetzky, B., and Devinsky, O., 2007, "Marijuana: an effective antiepileptic treatment in partial epilepsy? A case report and review of the literature.," Rev Neurol Dis, **4**(2), pp. 103–106.

[421] Mechoulam, R., and Carlini, E. A., 1978, "Toward drugs derived from cannabis," Naturwissenschaften, **65**(4), pp. 174–179.

[422] Carlini, E. A., and Cunha, J. M., 1981, "Hypnotic and antiepileptic effects of cannabidiol.," J Clin Pharmacol, **21**(8-9 Suppl), pp. 417S–427S.

[423] Cunha, J. M., Carlini, E. A., Pereira, A. E., Ramos, O. L., Pimentel, C., Gagliardi, R., Sanvito, W. L., Lander, N., and Mechoulam, R., 1980, "Chronic administration of cannabidiol to healthy volunteers and epileptic patients.," Pharmacology, **21**(3), pp. 175–185.

[424] Trembly, B., and Sherman, M., 1990, Double-blind clinical study of cannabidiol as a secondary anticonvulsant, Marijuana.

[425] Ames, F. R., and Cridland, S., 1986, "Anticonvulsant effect of cannabidiol.," S. Afr. Med. J., **69**(1), p. 14.

[426] Hagerty, S. L., YorkWilliams, S. L., Mittal, V. A., and Hutchison, K. E., 2015, "The cannabis conundrum: Thinking outside the THC box.," The Journal of Clinical Pharmacology, pp. n/a–n/a.

[427] Besag, F. M., 2001, "Behavioural effects of the new anticonvulsants.," Drug Safety, **24**(7), pp. 513–536.

[428] Merritt, J. C., Crawford, W. J., Alexander, P. C., Anduze, A. L., and Gelbart, S. S., 1980, "Effect of marihuana on intraocular and blood pressure in glaucoma.," Ophthalmology, **87**(3), pp. 222–228.

[429] Merritt, J. C., Olsen, J. L., Armstrong, J. R., and McKinnon, S. M., 2011, "Topical Δ9-tetrahydrocannabinol in hypertensive glaucomas," Journal of Pharmacy and Pharmacology, **33**(1), pp. 40–41.

[430] Roitman, P., Mechoulam, R., Cooper-Kazaz, R., and Shalev, A., 2014, "Preliminary, Open-Label, Pilot Study of Add-On Oral Δ9-Tetrahydrocannabinol in Chronic Post-Traumatic Stress Disorder," Clinical Drug Investigation, **34**(8), pp. 587–591.

[431] Fraser, G. A., 2009, "The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD)," CNS Neuroscience & Therapeutics, **15**(1), pp. 84–88.

[432] Jetly, R., Heber, A., Fraser, G., and Boisvert, D., 2015, "The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: A preliminary randomized, double-blind, placebo-controlled cross-over design study.," Psychoneuroendocrinology, **51**, pp. 585–588.

[433] Mashiah, M., 2012, Medical cannabis as treatment for chronic combat PTSD: Promising results in an open pilot study, Presentation at Patients Out of Time Conference.

[434] Rudolf Schicho, M. S., 2014, "Cannabis finds its way into treatment of Crohn's disease," Pharmacology, **93**(0), pp. 1–3.

[435] Schicho, R., and Storr, M., 2014, "IBD: Patients with IBD find symptom relief in the Cannabis field.," Nat Rev Gastroenterol Hepatol, **11**(3), pp. 142–143.

[436] Naftali, T., Bar-Lev Schleider, L., Dotan, I., Lansky, E. P., Sklerovsky Benjaminov, F., and Konikoff, F. M., 2013, "Cannabis Induces a Clinical Response in Patients With Crohn's Disease: A Prospective Placebo-Controlled Study," Clinical Gastroenterology and Hepatology, **11**(10), pp. 1276–1280.e1.

[437] T, N., R, M., LB, L., and FM, K., 2013, "Cannabis for inflammatory bowel disease.," Dig Dis, **32**(4), pp. 468–474.

[438] Pertwee, R. G., 2001, "Cannabinoids and the gastrointestinal tract.," Gut, **48**(6), pp. 859–867.

[439] Nasser, Y., Bashashati, M., and Andrews, C. N., 2014, "Toward modulation of the endocannabinoid system for treatment of gastrointestinal disease: FAAHster but not 'higher'," Neurogastroenterology & Motility, **26**(4), pp. 447–454.

[440] Di Carlo, G., and Izzo, A. A., 2003, "Cannabinoids for gastrointestinal diseases: potential therapeutic applications.," Expert Opin Investig Drugs, **12**(1), pp. 39–49.

[441] Spithoff, S., Emerson, B., and Spithoff, A., 2015, "Cannabis legalization: adhering to public health best practice.," CMAJ, **187**(16), pp. 1211–1216.

[442] Knopf, A., 2015, "New ICD-10 codes distinguish between use, abuse, dependence," Alcoholism & Drug

Abuse Weekly, **27**(38), pp. 5–6.

[443] Wish, E. D., 1990, "Preemployment Drug Screening," JAMA: The Journal of the American Medical Association, **264**(20), pp. 2676–2677.

[444] Gorman, D. M., and Derzon, J. H., 2002, "Behavioral traits and marijuana use and abuse: a meta-analysis of longitudinal studies," Addictive Behaviors, **27**(2), pp. 193–206.

[445] Swift, W., Hall, W., and Teesson, M., 2001, "Cannabis use and dependence among Australian adults: results from the National Survey of Mental Health and Wellbeing," Addiction, **96**(5), pp. 737–748.

[446] Mikulich, S. K., Hall, S. K., Whitmore, E. A., and Crowley, T. J., 2001, "Concordance between DSM-III-R and DSM-IV diagnoses of substance use disorders in adolescents.," Drug and Alcohol Dependence, **61**(3), pp. 237–248.

[447] Price, R. K., Risk, N. K., and Spitznagel, E. L., 2001, "Remission from drug abuse over a 25-year period: patterns of remission and treatment use," American Journal of Public Health, **91**(7), pp. 1107–1113.

[448] Price, M. R., 2005, "Allosteric Modulation of the Cannabinoid CB1 Receptor," Molecular Pharmacology, **68**(5), pp. 1484–1495.

[449] Miller, P., and Plant, M., 2002, "Heavy cannabis use among UK teenagers: an exploration.," Drug and Alcohol Dependence, **65**(3), pp. 235–242.

[450] Degenhardt, L., Hall, W., and Lynskey, M., 2001, "Alcohol, cannabis and tobacco use among Australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis," Addiction, **96**(11), pp. 1603–1614.

[451] Degenhardt, L., and Hall, W., 2001, "The association between psychosis and problematical drug use among Australian adults: findings from the National Survey of Mental Health and Well-Being," Psychol Med, **31**(04), pp. 659–668.

[452] Peretti-Watel, P., Beck, F., and Legleye, S., 2002, "Beyond the U-curve: the relationship between sport and alcohol, cigarette and cannabis use in adolescents," Addiction, **97**(6), pp. 707–716.

[453] MCDANIEL, M. A., 1988, "DOES PRE-EMPLOYMENT DRUG USE PREDICT ON-THE-JOB SUITABILITY?," Personnel Psychology, **41**(4), pp. 717–729.

[454] Blank, D. L., Fenton, J. W., US Department of Health and Human Services; National Institute on Drug Abuse, "Early Employment Testing for Marijuana: Demographic and Employee Retention Patterns."

[455] Parish, D. C., 1989, "Relation of the pre-employment drug testing result to employment status," Journal of General Internal Medicine, **4**(1), pp. 44–47.

[456] Normand, J., Salyards, S. D., and Mahoney, J. J., 1990, "An evaluation of preemployment drug testing.," Journal of Applied Psychology, **75**(6), pp. 629–639.

[457] Zwerling, C., 1990, "The Efficacy of Preemployment Drug Screening for Marijuana and Cocaine in Predicting Employment Outcome," JAMA, **264**(20), pp. 2639–2643.

[458] Ryan, J., Zwerling, C., and Jones, M., 1992, "The Effectiveness of Preemployment Drug Screening in the Prediction of Employment Outcome," J. Occup. Environ. Med., **34**(11), pp. 1057–1063.

[459] Braun, B. L., Hannan, P., Wolfson, M., Jones-Webb, R., and Sidney, S., 2000, "Occupational attainment, smoking, alcohol intake, and marijuana use," Addictive Behaviors, **25**(3), pp. 399–414.

[460] 2002, "Cannabis and Cannabinoids."

[461] Lowenstein, S. R., and Koziol-McLain, J., 2001, "Drugs and Traffic Crash Responsibility: A Study of Injured Motorists in Colorado," Journal of Trauma and Acute Care Surgery, **50**(2), p. 313.

[462] Braun, B. L., Tekawa, I. S., Gerberich, S. G., and Sidney, S., 1998, "Marijuana Use and Medically Attended Injury Events," Annals of Emergency Medicine, **32**(3), pp. 353–360.

[463] Sydow, von, K., Lieb, R., Pfister, H., Höfler, M., Sonntag, H., and Wittchen, H.-U., 2001, "The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study of adolescents and young adults," Drug and Alcohol Dependence, **64**(3), pp. 347–361.

[464] Sydow, von, K., Lieb, R., Pfister, H., Höfler, M., Sonntag, H., and Wittchen, H.-U., 2001, "The natural course of cannabis use, abuse and dependence over four years: a longitudinal community study of adolescents and young adults," Drug and Alcohol Dependence, **64**(3), pp. 347–361.

[465] Felder, C. C., and Glass, M., 2003, "CANNABINOID RECEPTORS AND THEIR ENDOGENOUS AGONISTS," http://dx.doi.org/10.1146/annurev.pharmtox.38.1.179, **38**(1), pp. 179–200.

[466] Tanda, G., Pontieri, F. E., and Di Chiara, G., 1997, "Cannabinoid and Heroin Activation of Mesolimbic Dopamine Transmission by a Common μ1 Opioid Receptor Mechanism," Science, **276**(5321), pp. 2048–2050.

[467] McGregor, I. S., Issakidis, C. N., and Prior, G., 1996, "Aversive effects of the synthetic cannabinoid CP 55,940 in rats," Pharmacol. Biochem. Behav., **53**(3), pp. 657–664.

[468] Parker, L. A., and Gillies, T., 1995, "THC-induced place and taste aversions in Lewis and Sprague-Dawley rats.," Behav. Neurosci., **109**(1), pp. 71–78.

[469] Onaivi, E. S., Green, M. R., and Martin, B. R., 1990, "Pharmacological characterization of cannabinoids in the elevated plus maze.," Journal of Pharmacology and Experimental Therapeutics, **253**(3), pp. 1002–1009.

[470] McGregor, I. S., Bryant, P. A., and Arnold, J., 1995, CP55, 940, a synthetic cannabinoid, does not sensitize locomotor activity or cocaine responsitivity with intermittent administration in Wistar rats, Soc. Neurosci. Abstr.

[471] Leite, J. R., and Carlini, E. A., 1974, "Failure obtain ?cannabis-directed behavior? and abstinence syndrome in rats chronically treated with Cannabis sativa extracts," Psychopharmacologia, **36**(2), pp. 133–145.

[472] Harris, R. T., Waters, W., and McLendon, D., 1974, "Evaluation of reinforcing capability of delta-9-tetrahydrocannabinol in rhesus monkeys," Psychopharmacologia, **37**(1), pp. 23–29.

[473] Takahashi, R. N., and Singer, G., 1981, "Cross self-administration of delta 9-tetrahydrocannabinol and D-amphetamine in rats.," Braz. J. Med. Biol. Res., **14**(6), pp. 395–400.

[474] Glass, M., and Felder, C. C., 1997, "Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1

receptor.," J. Neurosci., **17**(14), pp. 5327–5333.

[475] Corcoran, M. E., and Amit, Z., 1974, "Reluctance of rats to drink hashish suspensions: Free-choice and forced consumption, and the effects of hypothalamic stimulation," Psychopharmacologia, **35**(2), pp. 129–147.

[476] Wachtel, S., ElSohly, M., Ross, S., Ambre, J., and De Wit, H., 2002, "Comparison of the subjective effects of Δ9-tetrahydrocannabinol and marijuana in humans," Psychopharmacology, **161**(4), pp. 331–339.

[477] 1999, "Marijuana Made Easy: Armies of Experts Sell a Little White Pill."

[478] Golub, A., and Johnson, B. D., 2001, "Variation in youthful risks of progression from alcohol and tobacco to marijuana and to hard drugs across generations.," American Journal of Public Health, **91**(2), pp. 225–232.

[479] Mackesy-Amiti, M. E., Fendrich, M., and Goldstein, P. J., 1997, "Sequence of drug use among serious drug users: typical vs atypical progression.," Drug and Alcohol Dependence, **45**(3), pp. 185–196.

[480] Russo, E. B., Guy, G. W., and Robson, P. J., 2007, "Cannabis, Pain, and Sleep: Lessons from Therapeutic Clinical Trials ofSativex®, a Cannabis-Based Medicine," Chemistry & Biodiversity, **4**(8), pp. 1729–1743.

[481] Wells, K., "Pediatric Marijuana Exposure DDHS Training August 11, 2015."

[482] Warshak, C. R., Regan, J., Moore, B., Magner, K., Kritzer, S., and Van Hook, J., 2015, "Association between marijuana use and adverse obstetrical and neonatal outcomes," Nature Publishing Group, pp. 1–5.

[483] Fride, E., Ginzburg, Y., Breuer, A., Bisogno, T., Di Marzo, V., and Mechoulam, R., 2001, "Critical role of the endogenous cannabinoid system in mouse pup suckling and growth.," European Journal of Pharmacology, **419**(2-3), pp. 207–214.

[484] Fride, E., 2004, "The Endocannabinoid-CB Receptor System: Importance for development and in pediatric disease," nel.edu.

[485] Jin, K., Xie, L., Kim, S. H., Parmentier-Batteur, S., Sun, Y., Mao, X. O., Childs, J., and Greenberg, D. A., 2004, "Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice.," Molecular Pharmacology, **66**(2), pp. 204–208.

[486] Puente, N., Elezgarai, I., Lafourcade, M., Reguero, L., Marsicano, G., Georges, F., Manzoni, O. J., and Grandes, P., 2010, "Localization and function of the cannabinoid CB1 receptor in the anterolateral bed nucleus of the stria terminalis.," PLoS ONE, **5**(1), p. e8869.

[487] McPartland, J. M., Guy, G. W., and Di Marzo, V., 2014, "Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system.," PLoS ONE, **9**(3), p. e89566.

[488] Fride, E., Foox, A., Rosenberg, E., and Faigenboim, M., 2003, "Milk intake and survival in newborn cannabinoid CB 1 receptor knockout mice: evidence for a 'CB 3' receptor," European journal of ….

[489] Bendersky, M., Alessandri, S., Gilbert, P., and Lewis, M., 1996, "Characteristics of pregnant substance abusers in two cities in the northeast.," The American Journal of Drug and Alcohol Abuse, **22**(3), pp. 349–362.

[490] Russo, E., 2002, "Cannabis treatments in obstetrics and gynecology: A historical review," Journal of Cannabis therapeutics, **2**(3-4), pp. 5–35.

[491] Wilcox, A. J., Weinberg, C. R., and Baird, D. D., 1990, "Risk Factors for Early Pregnancy Loss," Epidemiology, **1**(5), pp. 382–385.

[492] Fried, P. A., WATKINSON, B., DILLON, R. F., and DULBERG, C. S., 1987, "Neonatal Neurological Status in a Low-Risk Population after Prenatal Exposure to Cigarettes, Marijuana, and Alcohol," Journal of Developmental & Behavioral Pediatrics, **8**(6), p. 318???326.

[493] Witter, F., and Niebyl, J., 2008, "Marijuana Use in Pregnancy and Pregnancy Outcome," American Journal of Perinatology, **7**(01), pp. 36–38.

[494] Parker, S. J., and Zuckerman, B. S., 1999, "The Effects of Maternal Marihuana Use During Pregnancy on Fetal Growth," Marihuana and Medicine, G.G. Nahas, K.M. Sutin, D. Harvey, S. Agurell, N. Pace, and R. Cancro, eds., Humana Press, Totowa, NJ, pp. 461–466.

[495] Linn, S., Schoenbaum, S. C., Monson, R. R., Rosner, R., Stubblefield, P. C., and Ryan, K. J., 1983, "The association of marijuana use with outcome of pregnancy.," American Journal of Public Health, **73**(10), pp. 1161–1164.

[496] Dreher, M. C., Nugent, K., and Hudgins, R., 1994, "Prenatal marijuana exposure and neonatal outcomes in Jamaica: an ethnographic study.," Pediatrics, **93**(2), pp. 254–260.

[497] Dreher, M. C., 1997, Cannabis and pregnancy, Cannabis in medical practice: A legal.

[498] Fride, E., 2004, "The endocannabinoid-CB1 receptor system in pre- and postnatal life," European Journal of Pharmacology, **500**(1-3), pp. 289–297.

[499] Fride, E., and Mechoulam, R., 1996, "Developmental aspects of anandamide: ontogeny of response and prenatal exposure.," Psychoneuroendocrinology, **21**(2), pp. 157–172.

[500] Abrahamov, A., and Mechoulam, R., 1995, "An efficient new cannabinoid antiemetic in pediatric oncology.," Life Sciences, **56**(23-24), pp. 2097–2102.

[501] Kim, H. S., Hall, K. E., Genco, E. K., Van Dyke, M., Barker, E., and Monte, A. A., 2016, "Marijuana Tourism and Emergency Department Visits in Colorado.," N. Engl. J. Med., **374**(8), pp. 797–798.

[502] Hudak, M., Severn, D., and Nordstrom, K., 2015, "Edible Cannabis-Induced Psychosis: Intoxication and Beyond.," Am J Psychiatry, **172**(9), pp. 911–912.

[503] Sewell, R. A., Poling, J., and Sofuoglu, M., 2009, "The Effect of Cannabis Compared with Alcohol on Driving," American Journal on Addictions, **18**(3), pp. 185–193.

[504] Andrews, R., Murphy, K. G., Nahar, L., and Paterson, S., 2015, "Cannabinoid concentrations detected in fatal road traffic collision victims compared with a population of other postmortem cases.," Clinical Chemistry, **61**(10), pp. 1256–1264.

[505] Ramaekers, J. G., 2003, "Antidepressants and driver impairment: empirical evidence from a standard on-the-road test.," J Clin Psychiatry, **64**(1), pp. 20–29.

[506] Verster, J. C., and Roth, T., 2013, "Blood drug concentrations of benzodiazepines correlate poorly with

actual driving impairment.," Sleep Medicine Reviews, **17**(2), pp. 153–159.

[507] Verster, J. C., and Roth, T., 2012, "The prevalence and nature of stopped on-the-road driving tests and the relationship with objective performance impairment," Accid Anal Prev, **45**, pp. 498–506.

[508] Jones, A. W., Holmgren, A., and Kugelberg, F. C., 2008, "Driving under the influence of cannabis: a 10-year study of age and gender differences in the concentrations of tetrahydrocannabinol in blood," Addiction, **103**(3), pp. 452–461.

[509] Jones, G. R., 1998, Interpretation of postmortem drug levels, Drug abuse handbook. CRC Press.

[510] Hoffman, J. M., Tran, V., Wachtman, L. M., Green, C. L., Jones, D. P., and Promislow, D. E. L., 2016, "A longitudinal analysis of the effects of age on the blood plasma metabolome in the common marmoset, Callithrix jacchus.," Exp. Gerontol., **76**, pp. 17–24.

[511] Drummer, O. H., 2005, "Review: Pharmacokinetics of illicit drugs in oral fluid," Forensic Science International, **150**(2-3), pp. 133–142.

[512] Drummer, O. H., and Yap, S., 2016, "The involvement of prescribed drugs in road trauma.," Forensic Science International, **265**, pp. 17–21.

[513] Musshoff, F., Padosch, S., Steinborn, S., and Madea, B., 2004, "Fatal blood and tissue concentrations of more than 200 drugs.," Elsevier Ireland Ltd, **142**(2-3), pp. 161–210.

[514] Jönsson, A. K., Söderberg, C., Espnes, K. A., Ahlner, J., Eriksson, A., Reis, M., and Druid, H., 2014, "Sedative and hypnotic drugs--fatal and non-fatal reference blood concentrations.," Forensic Science International, **236**, pp. 138–145.

[515] Verstraete, A. G., 2005, "Oral fluid testing for driving under the influence of drugs: history, recent progress and remaining challenges," Forensic Science International, **150**(2-3), pp. 143–150.

[516] Spiehler, V., Baldwin, D., and Hand, C., 1999, "Cut-off concentrations for drugs of abuse in saliva for DUI, DWI or other driving-related crimes," report presented at the ….

[517] Wood, E., Brooks-Russell, A., and Drum, P., 2015, "Delays in DUI blood testing: Impact on cannabis DUI assessments," Traffic Inj Prev, **17**(2), pp. 105–108.

[518] Laino, C., "Drug Tests Not Immune from False Positives," CBSnews.com [Online]. Available: http://www.cbsnews.com/news/drug-tests-not-immune-from-false-positives/. [Accessed: 14-May-2016].

[519] "Employment-Related Drug Testing | Drug War Facts," drugwarfacts.org [Online]. Available: http://www.drugwarfacts.org/cms/Drug_Testing_Employee. [Accessed: 14-May-2016].

[520] "Drug Testing in the Workplace," workrights.us [Online]. Available: http://workrights.us/?products=drug-testing-in-the-workplace. [Accessed: 14-May-2016].

[521] "Impairment Testing - Does it Work?," workrights.us [Online]. Available: http://workrights.us/?products=impairment-testing-does-it-work. [Accessed: 14-May-2016].

[522] Toennes, S. W., Kauert, G. F., Steinmeyer, S., and Moeller, M. R., 2005, "Driving under the influence of drugs -- evaluation of analytical data of drugs in oral fluid, serum and urine, and correlation with

impairment symptoms.," Elsevier Ireland Ltd, **152**(2-3), pp. 149–155.

[523] Hickox, S. A., 2011, "Drug testing of medical marijuana users in the workplace: an inaccurate test of impairment," Hofstra Lab & Emp LJ.

[524] Munsey, C., "Testing for impairment."

[525] Tanda, G., Munzar, P., and Goldberg, S. R., 2000, "Self-administration behavior is maintained by the psychoactive ingredient of marijuana in squirrel monkeys.," Nat. Neurosci., **3**(11), pp. 1073–1074.

[526] Berger, A., 2000, "Marijuana has potential for misuse," BMJ, **321**(7267), p. 979A.

[527] Lichtman, A. H., Sheikh, S. M., Loh, H. H., and Martin, B. R., 2001, "Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice.," Journal of Pharmacology and Experimental Therapeutics, **298**(3), pp. 1007–1014.

[528] Yamaguchi, T., Hagiwara, Y., Tanaka, H., Sugiura, T., Waku, K., Shoyama, Y., Watanabe, S., and Yamamoto, T., 2001, "Endogenous cannabinoid, 2-arachidonoylglycerol, attenuates naloxone-precipitated withdrawal signs in morphine-dependent mice," Brain Research, **909**(1-2), pp. 121–126.

[529] Valverde, O., Noble, F., Beslot, F., Dauge, V., Fournie-Zaluski, M.-C., and Roques, B. P., 2001, "Delta9-tetrahydrocannabinol releases and facilitates the effects of endogenous enkephalins: reduction in morphine withdrawal syndrome without change in rewarding effect," European Journal of Neuroscience, **13**(9), pp. 1816–1824.

[530] Brody, S., and Preut, R., 2002, "Cannabis, tobacco, and caffeine use modify the blood pressure reactivity protection of ascorbic acid," Pharmacol. Biochem. Behav., **72**(4), pp. 811–816.

[531] Stanley-Cary, C. C., Harris, C., and Martin-Iverson, M. T., 2002, "Differing effects of the cannabinoid agonist, CP 55,940, in an alcohol or Tween 80 solvent, on prepulse inhibition of the acoustic startle reflex in the rat," Behavioural Pharmacology, **13**(1), pp. 15–28.

[532] Giuffrida, A., Parsons, L. H., Kerr, T. M., Rodriguez de Fonseca, F., Navarro, M., and Piomelli, D., 1999, "Dopamine activation of endogenous cannabinoid signaling in dorsal striatum.," Nat. Neurosci., **2**(4), pp. 358–363.

[533] Piomelli, D., Giuffrida, A., Parsons, L. H., Rodriguez de Fonseca, F., and Navarro, M., 1999, "Dopamine activation of endogenous cannabinoid signaling in dorsal striatum," Prostaglandins Other Lipid Mediat., **59**(1-6), p. 51.

[534] Kouri, E. M., and Pope, H. G., 2000, "Abstinence symptoms during withdrawal from chronic marijuana use.," Experimental and Clinical Psychopharmacology, **8**(4), pp. 483–492.

[535] Smith, N. T., 2002, "A review of the published literature into cannabis withdrawal symptoms in human users," Addiction, **97**(6), pp. 621–632.

[536] Kleiber, D., Soellner, R., and Tossmann, P., 1997, Cannabiskonsum in der Bundesrepublik Deutschland, Entwicklungstendenzen.

[537] Hall, W. D., Room, R., and Bondy, S., 1999, Comparing the health and psychological risks of alcohol, cannabis, nicotine and opiate use, Addiction Research Foundation.

[538] Luthra, Y. K., Esber, H. J., Lariviere, D. M., and Rosenkrantz, H., 2008, "Assessment of Tolerance to Immunosuppressive Activity of Δ 9-Tetrahydrocannabinoll in Rats," Journal of Immunopharmacology, **2**(2), pp. 245–256.

[539] Hilts, P. J., and Henningfield, J. E., 1994, Is Nicotine Addictive, New York Times.

[540] Chen, K., Kandel, D. B., and Davies, M., 1997, "Relationships between frequency and quantity of marijuana use and last year proxy dependence among adolescents and adults in the United States.," Drug and Alcohol Dependence, **46**(1-2), pp. 53–67.

[541] Kandel, D., 1997, "Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the U.S. population," Drug and Alcohol Dependence, **44**(1), pp. 11–29.

[542] Crowley, T. J., Macdonald, M. J., Whitmore, E. A., and Mikulich, S. K., 1998, "Cannabis dependence, withdrawal, and reinforcing effects among adolescents with conduct symptoms and substance use disorders.," Drug and Alcohol Dependence, **50**(1), pp. 27–37.

[543] Mead, A., 2008, "International Control of Cannabis from Medicinal uses of cannabis and cannabinoids," pp. 1–30.

[544] American Herbal Products Association Cannabis Committee, 2014, Recommendations for Regulators – Cannabis Operations.

[545] Vandrey, R., Raber, J. C., Raber, M. E., Douglass, B., Miller, C., and Bonn-Miller, M. O., 2015, "Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products.," JAMA, **313**(24), pp. 2491–2493.

[546] Thomas, B. F., and ElSohly, M., 2015, The Analytical Chemistry of Cannabis, Elsevier.

[547] Johnson, R. E., 2015, "Hemp as an Agricultural Commodity," pp. 1–33.

[548] World Health Organization, 2003, WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants, Geneva: World Health Organization.

[549] World Health Organization, 2007, WHO guidelines on good manufacturing practices (GMP) for herbal medicines, Geneva : World Health Organization.

[550] McCutcheon, A. R., 2002, "An exploration of current issues in botanical quality: A discussion paper," Canada: Natural Health Products.

[551] Mead, W., 2013, "FDA dietary supplement GMP regulations," Dietary Supplement Good Manufacturing Practices, CRC Press, pp. 249–287.

[552] Lee, S., 2015, "US FDA's new guidance on product quality for botanical drugs," Planta Med.

[553] 2009, United Nations Office on Drugs and Crime. Recommended Methods for the Identification and Analysis of Cannabis and Cannabis Products, United Nations Publications.

[554] Jensen, E. L., and Roussell, A., 2016, "Field Observations of the Developing Legal Recreational Cannabis Economy in Washington State," International Journal of Drug Policy, **0**(0).

[555] Rabin, R. C., 2013, "Legalizing of marijuana raises health concerns," NY Times.

[556] Benmaamar, R., 2014, "Colorado: a first in the USA for legal sale of marijuana," Lancet Oncol., **15**(2), p. e55.

[557] Kuehn, B. M., 2014, "Colorado Tackles Medical Implications of Marijuana," JAMA, **311**(20), pp. 2053–2054.

[558] Monte, A. A., Zane, R. D., and Heard, K. J., 2015, "The Implications of Marijuana Legalization in Colorado," JAMA, **313**(3), pp. 241–242.

[559] Silvers, W. S., 2016, "A Colorado allergist's experience with marijuana legalization," Annals of Allergy, Asthma & Immunology, **116**(2), pp. 175–177.

[560] Kamin, S., 2015, "Marijuana Legalization in Colorado -- Lessons for Colombia," SSRN Electronic Journal.