J

SECRETARIA DE SALUD

SUBSECRETARIA DE REGULACION Y FOMENTO SANITARIO
DIRECCION GENERAL DE CONTROL SANITARIO
DE BIENES Y SERVICIOS

AUTORIZACION SANITARIA DE IMPORTACION

No. DE AUTORIZACION
95107662- 2

ADUANA DE INTERNACION: AEROPUERTO INT. DE LA CD. DE MEXICO

CON FUNDAMENTO EN LOS ARTICULOS 39 FRACC. XII Y XXI DE LA LEY ORGANICA DE LA ADMINISTRACION PUBLICA FEDERAL. 194, 283, 284, 286 Y 369 DE LA LEY GENERAL DE SALUD, 129, 131 Y 155 DEL REGLAMENTO DE LA LEY GENERAL DE SALUD EN MATERIA DE CONTROL SANITARIO, ACTIVIDADES, ESTABLECIMIENTOS, PRODUCTOS Y SERVICIOS. ART. 13 FRACC. II DEL REGLAMENTO INTERIOR DE LA SECRETARIA DE SALUD, SE EXPIDE LA PRESENTE AUTORIZACION EN FAVOR DE :

NOMBRE O RAZON SOCIAL SUNRIDER MEXICO INC.

REGISTRO FEDERAL DE CONTRIBUYENTES SMI 9207318V8

DESCRIPCION DE LA MERCANCIA	FRACCION	CLAVE DE LOTE	CANTIDAD	UNIDAD	VALOR M.E.
EVERGREEN, EVERGREEN	21069099	812724A1	23.00	PAQUETES	158.47
EVERGREEN, EVERGREEN	21069099	813044A1	92.00	PAQUETES	633.88
CALLI BEVERAGE, CALLI BEVERAGE	21069099	812724A4	239.00	PAQUETES	1818.14
CALLI BEVERAGE, CALLI BEVERAGE	21069099	813004A4	480.00	PAQUETES	2844.80
NUPLUS 42 COMBO, NUPLUS 42 COMBO	21069099	813474A1	518.00	PAQUETES	5166.30
LIQUI FIVE, LIQUI FIVE	21069099	813184A1	368.00	PAQUETES	2973.44
SUNECTAR, SUNECTAR	21069099	81319402	294.00	PAQUETES	464.52
SUNECTAR, SUNECTAR	21069099	81349402	1274.00	PAQUETES	2012.92

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REQUISITOS QUE SE DEBERAN CUMPLIR: Entrada sin muestreo.

EN CASO DE RECONOCIMIENTO ADUANAL DEBERA PRESENTAR EL ORIGINAL DEL CERTIFICADO DE LIBRE VENTA EXPEDIDO POR EL DEPARTAMENTO DE SALUD DEL ESTADO DE CALIFORNIA, ESTADOS UNIDOS CON FECHA 29 DE NOVIEMBRE DE 1994 QUE AMPARA LOS PRODUCTOS A IMPORTAR. ESTA AUTORIZACION ES VALIDA POR UNA SOLA VEZ. EL ORIGINAL DEBERA QUEDAR CON EL PEDIMENTO ADUANAL. ESTA AUTORIDAD SE RESERVA FACULTADES QUE LE OTORGA LA LEY PARA LA EVALUACION POSTERIOR DE SUS PRODUCTOS. EN CONFORMIDAD CON LOS ARTICULOS 216, 286, 370 DE LA LEY GENERAL DE SALUD Y 65 DE SU REGLAMENTO EN LA MATERIA. EN PROXIMAS IMPORTACIONES SU CERTIFICADO DE ORIGEN DEBERA ESPECIFICAR Y AMPARAR CADA UNO DE LOS PRODUCTOS A IMPORTAR.

ATENTAMENTE
SUFRAGIO EFECTIVO NO REELECCION
EL DIRECTOR GENERAL

VIGENCIA | FECHA DE EXPEDICION: 19-01-95

agosto de 1994

de importación y de

Lunes 29 de agosto de 1994 DIARIO OFICIAL (Segunda Sección) 85

2106.80.99 Las demás.

de coadyuvar en los
s funciones para la
alcohólicas, bebidas
os que se utilizan en
ntidades federativas
culte en el futuro el

coadyuvar a que se
consideró sujetar a
a alimentos, bebidas

de las operaciones
a que se refiere el
mpuesto General de

portación temporal y
comprendidas en las
e indican, incluyendo

dos de Salud Pública
nos de las entidades
an las autorizaciones

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Unicamente. Complementos alimenticios de cualquier tipo a base de productos vegetales, de [illegible]es o extractos de origen vegetal o animal o similares o equivalente[illegible] sus mezclas a excepción de aquéllos considerados medicamentos.

II.- La Dirección General de Control de Insumos para la Salud expedirá las autorizaciones previas de importación de las siguientes fracciones arancelarias:

1211.90.03	2937.29.05	2939.29.01	3003.40.03
1211.90.99	2937.91.01	2939.30.01	3003.40.99
1302.11.01	2937.91.02	2939.40.01	3003.90.02
1302.11.03	2937.92.01	2939.60.01	3003.90.03
1302.11.99	2937.92.02	2939.90.01	3003.90.05
1302.14.99	2937.92.03	2939.90.03	3003.90.06
1302.19.09	2937.92.04	2939.90.05	3003.90.07
1302.19.99	2937.92.05	2939.90.07	3003.90.09
2202.90.01	2937.92.06	2939.90.12	3003.90.10
2811.29.01	2937.92.07	2939.90.13	3003.90.12
2836.91.01	2937.92.08	2939.90.16	3003.90.14
2844.40.01	2937.92.09	2941.10.01	3003.90.15
2844.40.02	2937.92.10	2941.10.02	3003.90.16
2844.40.99	2937.92.11	2941.10.03	3003.90.18
2845.90.99	2937.92.12	2941.10.04	3003.90.99
2850.00.99	2937.92.13	2941.10.05	3004.10.01
2905.11.01	2937.92.14	2941.10.06	3004.20.01
2910.90.99	2937.92.15	2941.10.07	3004.31.99
2913.00.01	2937.92.16	2941.10.08	3004.32.01
2915.90.07	2937.92.17	2941.10.09	3004.39.01
2915.90.21	2937.92.18	2941.10.10	3004.39.99
2921.19.11	2937.92.19	2941.10.11	3004.40.03
2921.49.02	2937.92.20	2941.10.99	3004.40.99
2921.49.09	2937.92.99	2941.20.01	3004.50.01
2922.19.08	2937.99.01	2941.30.01	3004.50.02
2922.30.04	2937.99.02	2941.30.03	3004.50.99
2922.30.99	2937.99.03	2941.30.99	3004.90.02
2922.49.21	2937.99.04	2941.40.01	3004.90.03
2922.49.22	2937.99.05	2941.50.01	3004.90.06
2922.50.19	2937.99.06	2941.50.99	3004.90.08
2922.50.48	2937.99.08	2941.90.01	3004.90.10
2922.50.99	2937.99.11	2941.90.02	3004.90.12
2924.10.03	2937.99.12	2941.90.03	3004.90.13
2924.10.12	2937.99.13	2941.90.04	3004.90.14
2925.19.01	2937.99.14	2941.90.05	3004.90.15
2928.00.06	2937.99.16	2941.90.06	3004.90.16
2928.00.99	2937.99.10	2941.90.07	3004.90.17
2926.10.06	2937.99.21	2941.90.08	3004.90.18
2931.00.05	2937.99.22	2941.90.09	3004.90.19
2933.59.01	2937.99.23	2941.90.10	3004.90.20
2933.59.06	2937.99.25	2941.90.11	3004.90.21
2933.59.99	2937.99.27	2941.90.12	3004.90.99
2933.90.22	2937.99.28	2941.90.13	3006.10.01
2933.90.28	2937.99.29	2941.90.14	3006.10.02
2933.90.30	2937.99.30	2941.90.15	3006.10.99
2933.90.34	2937.99.32	2941.90.16	3006.20.01
2933.90.41	2937.99.33	2941.90.17	3006.20.99
2933.90.42	2937.99.34	2941.90.18	3006.30.01
2933.90.01	2937.99.35	2941.90.19	3006.30.02
2933.90.99	2937.99.36	2941.90.99	3006.40.01
2934.90.06	2937.99.39	3001.10.01	3006.40.03
2934.90.44	2937.99.40	3001.20.01	3504.00.03
2934.90.99	2937.99.41	3001.20.02	3802.10.01
2935.00.01	2937.99.99	3001.20.03	3802.90.01
2935.00.03	2938.10.01	3001.20.04	3823.90.06
2935.00.04	2938.90.03	3001.20.99	3913.90.03
2935.00.05	2938.90.04	3001.90.01	4014.10.01
2935.00.06	2938.90.05	3001.90.02	9018.19.05
2935.00.07	2938.90.06	3001.90.03	9018.19.07
2935.00.08	2938.90.08	3001.90.99	9018.19.08

Que la Ley General de Salud establece el control sanitario de los productos y materias primas de importación y de exportación por parte de la Secretaría de Salud;

Que el Programa Nacional de Salud 1990-1994 puntualiza como uno de sus objetivos básicos el de coadyuvar en los procesos de desconcentración y descentralización, por lo que la Secretaría de Salud desconcentró funciones para la tramitación y expedición de las autorizaciones [illegible]

[illegible] perfumería, belleza y aseo, tabaco, así como las materias primas y aditivos que se utilizan en su elaboración, medi[illegible] acuerdos 104, 111, 116 y de Coordinación con [illegible] gobiernos de las entidades federativas publicados en el Diario Oficial de la Federación, y en su caso, las entidades federativas que faculte en el futuro el Secretario de Salud;

Que para dar cumplimiento a lo establecido en la Ley de Comercio Exterior, y con el fin de coadyuvar a que se implemente la regulación por parte de la Secretaría de Salud, la Comisión de Comercio Exterior consideró sujetar a regulación la importación y exportación temporal y definitiva de productos y materias primas relativas a alimentos, bebidas alcohólicas y no alcohólicas, tabaco, de perfumería, belleza y aseo, así como de insumos para la salud;

Que con el objeto de mantener un marco regulatorio claro y transparente que permita la agilización de las operaciones del comercio exterior, se establece la clasificación y codificación de los productos y materias primas a que se refiere el considerando anterior, comprendidas en las fracciones arancelarias de las Tarifas de la Ley del Impuesto General de Importación y de la de Exportación, hemos tenido a bien expedir el siguiente

ACUERDO QUE ESTABLECE LA CLASIFICACIÓN Y CODIFICACION DE MERCANCIAS CUYA IMPORTACION O EXPORTACION ESTA SUJETA A REGULACION SANITARIA POR PARTE DE LA SECRETARIA DE SALUD

ARTICULO PRIMERO.- Se establece la clasificación y codificación de las mercancías cuya importación temporal y definitiva está sujeta a autorización sanitaria previa de importación por parte de la Secretaría de Salud, comprendidas en las fracciones arancelarias de la Tarifa de la Ley del Impuesto General de Importación que a continuación se indican, incluyendo la importación que de dichas mercancías se realice a la región fronteriza y franjas fronterizas del país:

I.- La Dirección General de Control Sanitario de Bienes y Servicios, así como los Servicios Coordinados de Salud Pública en los estados a que se refieren los acuerdos números 104, 111, 116 y de Coordinación con los gobiernos de las entidades federativas suscritos por el Secretario de Salud, en sus respectivos ámbitos de competencia, expedirán las autorizaciones sanitarias previas de importación de las siguientes fracciones arancelarias:

0301.91.01	0303.75.01	0307.51.01	1302.20.99
0301.92.01	0303.76.01	0307.59.99	1302.32.99
0301.93.01	0303.77.01	0307.60.01	1504.10.01
0301.99.99	0303.78.01	0307.91.01	1504.20.01
0302.11.01	0303.79.99	0307.99.99	1507.90.99
0302.12.01	0303.80.01	0401.10.01	1509.10.01
0302.19.99	0304.10.01	0401.10.99	1509.10.99
0302.21.01	0304.20.01	0401.20.01	1509.90.01
0302.22.01	0304.90.99	0401.20.99	1509.90.02
0302.23.01	0305.10.01	0401.30.01	1509.90.99
0302.29.99	0305.20.01	0401.30.99	1512.29.99
0302.31.01	0305.30.01	0402.10.01	1516.20.01
0302.32.01	0305.41.01	0402.10.99	1517.10.01
0302.33.01	0305.42.01	0402.21.01	1517.90.01
0302.39.99	0305.49.01	0402.21.99	1517.90.02
0302.40.01	0305.49.99	0402.29.99	1517.90.99
0302.50.01	0305.51.01	0402.91.01	1702.10.02
0302.61.01	0305.61.99	0402.91.99	1901.90.02
0302.62.01	0305.59.01	0402.99.01	2007.10.01
0302.63.01	0305.59.99	0402.99.99	2007.91.01
0302.64.01	0305.01.01	0403.10.01	2007.99.01
0302.65.01	0305.62.01	0403.90.01	2007.99.02
0302.66.01	0305.63.01	0403.90.99	2007.99.03
0302.69.01	0305.69.99	0404.10.01	2007.99.99
0302.69.99	0306.11.01	0404.90.99	2106.10.01
0302.70.01	0306.12.01	0405.00.01	2106.10.02
0303.10.01	0306.13.01	0405.00.02	2106.90.01
0303.21.01	0306.14.01	0405.00.03	3501.10.01
0303.22.01	0306.19.99	0405.00.99	3501.90.02
0303.29.99	0306.21.01	0406.10.01	3501.90.99
0303.31.01	0306.22.01	0406.20.01	3502.10.01
0303.32.01	0306.23.01	0406.30.01	3504.00.06
0303.33.01	0306.24.01	0406.30.99	3507.90.01
0303.39.99	0306.29.99	0406.40.01	3507.90.02
0303.41.01	0307.10.01	0406.90.01	3507.90.03
0303.42.01	0307.21.01	0406.90.02	3507.90.04
0303.43.01	0307.29.99	0406.90.03	3507.90.05
0303.49.01	0307.31.01	0406.90.04	3507.90.07
0303.50.01	0307.39.99	0406.90.05	3507.90.11
0303.60.01	0307.41.01	0406.90.06	3507.90.99
0303.71.01	0307.41.99	0406.90.99	6309.00.01
0303.72.01	0307.49.01	1211.20.01	9503.90.05
0303.73.01	0307.49.01	1212.20.01	----------
0303.74.01	0307.49.99	1302.12.99	----------

SUNRIDER INTERNATIONAL JAPAN K.K.
1-13-12 Higashi Gotanda 1-Chome
Shinagawa-ku, Tokyo 141, Japan
TEL. 03 3441 4300
FAX. 03-3473-5011

Sunrider International Japan
1-13-12, Higashi Gotanda , Shinagawa-ku, Tokyo 141 JAPAN
Tel: 01181-3-3441-4300
Fax: 01181-3-3473- 5011

FAX COVER MEMORANDUM

Date: March 29 , 1995
Ref.No. :95-0059

TO: Holly Vanderdonck - Legal Department

From: C.Tsuchihashi - Marketing Coordinator / Sunrider Japan

RE: Sunectar

Total No. of pages (including this page) 3

Dear Ms. Vanderdonck:

In response to your fax of MAR/27 regarding Sunectar, please find attached, Import Notification with a completion stamp from Quarantine station. The English translation of the format is also attached for your reference. Please note that in the Import Notification, Sunectar is classified as an additive (sweetener) .

If you have further inquiries, please do not hesitate to ask us.

Best regards,

C. Tsuchihashi

C. Tsuchihashi - Marketing Coordinator / Sunrider Japan

CC: R. Wennerholt - General Manager / Sunrider Japan

食品等輸入届書

厚生大臣殿

輸入者の氏名及び住所(法人の場合は、その名称及び所在地)
〒141 東京都品川区東五反田1-19-12
サンライダーインターナショナル・ジャパン株式会社
代表取締役 ルパート P. ウェナホルト
(電話)TEL 03 — 3441 — 4300

①生面届出	②計画輸入	③内訳	④継続	⑤検査

⑥届出受付番号 7769

※太ワク内は記入しないでください。

⑦品名コード	I1120
⑧積込重量	1 8 kg
⑨輸入者コード	35881
⑩生産国又は製造国 — 製造者コード	— / 304 999999
⑪通関港コード	1012
⑫到着年月日	平成 6年 6月 5日
⑬届出年月日	平成 6年 6月 7日

貨物の別	食品・添加物・器具・容器包装・おもちゃ
品名	甘味料 Sweetener
積込数量	1 Case(s)・B/C
包装の種類	PLASTIC BOTTLE
用途	COMMERCIAL
積込港	LOS ANGELES
積込年月日	平成 6年 6月 4日
積卸港	成田空港
貨物の記号及び番号	MARKS: AS. ADDR AWB NO: 01159748/003
船舶又は航空機 名称又は便名	KE0786
船舶又は航空機 国籍	
保管倉庫 名称及び所在地	B. TACT H/W 千葉県市川市原木2526
保管倉庫 搬入年月日	平成 6年 6月 7日
貨物(加工食品以外の食品を除く)の製造者又は加工者の氏名及び住所(法人の場合はその名称及び所在地)、並びに製造所又は加工所の名称及び所在地 加工食品以外の食品であるときはその生産地	SUNRIDER INTERNATIONAL U.S.A 3111 LOMITA BOULEVARD TORRANCE, CALIFORNIA U.S.A.
仕入書の記載内容	
事故の有無 あるときはその概要	有(無)

貨物が加工食品であるときは原材料及び製造又は加工の方法 貨物が器具、容器包装又はおもちゃであるときはその材質	別紙添付
貨物が化学的合成品たる添加物又は、規格基準の定められた天然添加物を含む食品である場合当該添加物の品名 貨物が化学的合成品を含む製剤の場合、その成分 (いずれの場合も栄養の目的で使用されるものを除く)	NIL

(備考)
SUNECTAR

HEI-WAKU TEL28-3121

Quarantine stations at Narita Airport, Baraki →
Stamp for completion of Food, etc, import notification ⑩

横由検印
成田空港検疫所
輸入食品等届出済
BARAKI

Import Notification Form

Ministry of Health and Welfare, Esq.

Name and address of importer
(In the case of corporation, its name and address:)

(Stamp)

(Telephone)

(1)	(2)	(3)	(4)	(5)
(6)				

Do not fill in the blanks in the bold frame.

(7) Code of article name	
(8) Weight of cargo	Kg
(9) Code of importer	
(10) Producing country or manufacturing country - Code of Manufacturer	
(11) Code of port for clearance	
(12) Date of arrival	
(13) Date of notification	

In the case of processed food, ingredients, and manufacturing or processing method In the case of apparatus, container-packages or toy, its materials	
In the case of chemically synthesized additives, or foods containing non-chemically synthesized additives for which specifications or standards are provided, name of the additives In the case of preparations containing chemical synthetics, their ingredients (In either cases excluding substances used for flavoring)	

Classification of cargo		Food, additives; apparatus container-packages or toys
Article name		
Quantity of cargo		C/S - C/T - B/G
Type of packing		
Use		
Port of shipment		
Date of shipment		year month day
Port for unloading		
Mark or number of cargo		
Ship Aircraft	Name or flight name	
Warehouse for storage	Name and address	
	Date of arrival of cargo	
In the case of processed food, name and address of manufacturer or processor (In the case of corporation, its name and address), and name and address of manufacturing or processing plant. In the case of foods other than processed foods: producing place		
Experience of accident, if any, its outline		

Note:

(14)

Stamp for completion of import notification

DEPARTEMEN KESEHATAN RI.
DIREKTORAT JENDERAL PENGAWASAN OBAT DAN MAKANAN
Jl. Percetakan Negara 23, Tromol Pos 143, Jakarta 10560, Telp. 411781, 415267

PERSETUJUAN PENDAFTARAN

No. 707/BB/Reg/ML/.1/91/805

Sesuai dengan Permenkes No. 382/MENKES/PER/VI/1989 tentang Pendaftaran Makanan dan SK Dirjen POM tentang Petunjuk Pelaksanaannya, dengan ini kami memberikan persetujuan pendaftaran makanan di bawah ini :

1.	Nama makanan	:	Food Supplement (Fruit Extracts)
2.	Nama dagang	:	SUNECTAR
3.	Jenis kemasan	:	Plastik
4a.	Nama pabrik/perusahaan	:	SUNRIDER INTERNATIONAL
b.	Alamat	:	3111 Lomita Boelevard Torrance California 90505
5a.	Nama perusahaan pemberi lisensi/perusahaah asal	:	-
b.	Alamat	:	-
6a.	Nama importir/perwakilan pabrik luar negeri	:	PT ASCOSO INDA AGUNG CORPORATION
b.	Alamat	:	Gedung BHA. Jl Wahid Hasyim No 76 Jakarta Pusat

dengan nomor pendaftaran

DEPKES RI. ML 62704030029

dan dengan label seperti terlampir.
Nomor pendaftaran ini berlaku untuk seterusnya dan dapat dicabut/dibatalkan sesuai dengan ketentuan yang berlaku.

Jakarta, 5 Nopember 1991
a.n. Direktur Jenderal Pengawasan
Obat dan Makanan
Kepala Direktorat Pengawasan
Makanan dan Minuman

Drs. [illegible] SURYANA

SUNRIDER THAILAND

31-Jan-95

PRODUCT REGISTRATIONS

PRODUCT TYPE	OLD COMPANY	REG. NO.	NEW COMPANY **	REG. NO.
FOOD	NUPLUS – ALL FLAVORS (5 ITEMS)	58–52/32	NUPLUS – ALL FLAVORS (6 ITEMS)	219–224/36
	SUNRIDER VITALITE I (ACTION CAPS)	57/32	SUNRIDER VITALITE I	30/36
	SUNRIDER VITALITE DELIGHT (FORTUNE DELIGHT)	S.D.3/2539	VITALITE DELIGHT	S.D.15/2537
	SUNNECTAR(SUNCARE)	S.D.17/2532	VITALITE DELIGHT – Cinnamon	S.D.91/2537
			– Lemon	S.D.92/2537
			VITAFRUIT	S.D.60/2537
			• SUNNY DAYS HONEY & LEMON	27/36
			• SUNNY DAYS HONEY & ORANGE	28/36
			• SUNBAR WITH HONEY	S.G.3/2537
			• MANGO SUNBAR WITH HONEY	S.G.9/2537
			• CHERRY SUNBAR WITH HONEY	S.G.8/2537
			• PINEAPPLE SUNBAR WITH HONEY	S.G.24/2537
			• BANANA SUNBAR WITH HONEY	S.G.25/2537
			• DR.CHEN'S SECRET SAUCE	4/37
	TOTAL 8 ITEMS		TOTAL 16 ITEMS	
TRADITIONAL MEDICINE	CONCO	K19/32	CONCO	K19/37
	PRIME AGAIN	K20/32	PRIME AGAIN	K20/37
	ASSIMILAID	K21/32	ASSIMILAID	K23/37
	ALPHA 20 C	K22/32	ALPHA 20 C	K 1/37
	JOI	K25/32	JOI	K 1/37
	ESE	K25/32	ESE	K 9/37
	QUINARY	K27/32	QUINARY	K21/37
	FIBERTONE	K28/32		
	DANDELION	K29/32	DANDELION	K 2/37
	KOREAN WHITE GINSENG	K31/32	KOREAN WHITE GINSENG	K 8/37
	SIBERIAN GINSENG	K31/32	SIBERIAN GINSENG	K 7/37
	GOLDEN SEAL	K32/32	GOLDEN SEAL	K 3/37
	WHITE WILLOW	K33/32	WHITE WILLOW	K 6/37
	TOP	K35/32	TOP	K 5/37
	CALLI	K38/32	CALLI	K 0/37
	DONG QUAI	K39/32	DONG QUAI	K 4/37
	B.G.P.	K43/32	B.G.P.	K22/37
	LSTREAM	K44/32	LSTREAM	K 4/37
	VITA TASTE	K45/32	VITA TASTE	K 7/37
	SUNRIDER VITALITE II, III(ACTION CAPS)	K 3&5/33	SUNRIDER VITALITE II, III(ACTION CAPS)	K 26 16/37
	SUNBREEZE OIL	K10/33	SUNBREEZE OIL	K 8/37
	SUNBREEZE BALM	K 4/34	SUNBREEZE BALM	K 6/37
	TOTAL 23 ITEMS		TOTAL 22 ITEMS	

• not yet been sold in Thailand

** registration in progress : Action cap & Vitalite Bar

SUNRIDER INTERNATIONAL
1625 Abalone Avenue
Torrance, CA 90501
Ph: (310) 781-3808
Legal Department
Fax: (310) 222-0275

July 27, 1995

Ms. Ruth Bandler
Office of Special Nutritionals
U.S. Food & Drug Administration (HFS-456)
FB8, Room 2804
200 C Street, S.W.
Washington, D.C. 20204

Re: Stevia rebaudiana bertoni
Use as a Dietary Supplement Ingredient

Dear Ms. Bandler:

Pursuant to the request of your office, enclosed herewith is a full and complete copy of the Food Ingredient Safety Review, *Stevia rebaudiana leaves*, prepared for the Herb Research Foundation by A. Douglas Kinghorn, Ph.D. Please note that this safety review was attached in part as Exhibit "H" to Sunrider International's July 7, 1995 letter for consideration of Stevia as a grandfathered old dietary ingredient, or in the alternative, a 75 day notification of The Sunrider Corporation dba Sunrider International's intent to market Stevia.

Should you have any questions or further comments, please do not hesitate to contact me.

Thank you for your assistance in this matter.

Very truly yours,
SUNRIDER INTERNATIONAL

Holly A Vanderdonck

Holly A. Vanderdonck
Associate Counsel

HAV:kdm
Enclosure

cc: Patrick Noonan, Esq. (w/encl.)

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Food Ingredient Safety Review

Stevia rebaudiana leaves

Prepared for Herb Research Foundation

by

A. Douglas Kinghorn, Ph.D.
Professor of Pharmacognosy
College of Pharmacy
University of Illinois at Chicago
Chicago, IL 60612

March 16, 1992

OUTLINE

SUMMARY AND CONCLUSIONS

1. *Stevia rebaudiana*, a plant native to Paraguay and Brazil, is the source of the highly sweet diterpene glycoside, stevioside, in addition to other sweet substances, such as rebaudioside A. Extracts of *S. rebaudiana* and/or stevioside, are currently approved as sweetening agents or food additives in Japan, Brazil, and South Korea. Products from this plant are used as herbal preparations in Paraguay and the People's Republic of China, and have also been available for sale in the United States for several years.

2. Among certain indigenous peoples of Paraguay, *Stevia rebaudiana* has been employed to sweeten bitter-tasting beverages and tobacco for centuries, and has been consumed there as an ingredient of medicinal herbal teas for over 40 years.

3. Since the 1970s, *Stevia rebaudiana* extracts and purified stevioside have been utilized in Japan for sweetening foodstuffs and beverages, and in 1988 such products constituted the largest component of the "high-intensity" sweetener market in that country, with 41% of the total market share. There are now over 70 *S. rebaudiana*-containing products on the Japanese market.

4. In the late 1980s, *Stevia rebaudiana* extracts and stevioside (devoid of certain hydrolytic products) were approved in Brazil for the flavoring and sweetening of various classes of foods, in addition to soft drinks.

5. Stevioside, the major sweet diterpene glycoside constituent of *Stevia rebaudiana* leaves, has several desirable properties not associated with most "high-intensity" sucrose substitutes, in that it is stable to acids and heat, and nonfermentive. It does not tend to discolor when heated, and has acceptable hedonic properties.

6. Despite there having been an estimated Japanese consumption of stevioside of over 85 metric tons in 1987 (a figure increasing annually), there have been no adverse reactions reported in the medical or scientific literature as a consequence. Since no negative clinical reports have appeared as a result of the consumption of *Stevia rebaudiana* products in any of the countries where they are available, it may be concluded that, on the basis of these observations, these materials present virtually no toxicity risk to humans.

7. It is estimated that there have been well over 500 scientific articles on *Stevia rebaudiana* and its sweet diterpene glycoside constituents. These articles comprise reviews, research papers, and patented procedures. Included are reports on the chemical analysis, cultivation, phytochemistry, purification methods, safety assessment, and sensory enhancement procedures for *S. rebaudiana* and its sweet principles.

8. Crude and purified *Stevia rebaudiana* extracts have been tested for acute and subacute toxicity in rodents, and may be considered safe for human consumption on the basis of this work.

9. In a chronic toxicity study carried out in Japan, wherein male and female rats were fed *Stevia rebaudiana* extracts for up to two years, no significant dose-dependent changes were found in relation to test animal appearance, growth, hematological or blood biochemical values, and the weights and macroscopic and microscopic characteristics of excised organs. Neoplasms that were observed were not attributable to the administration of *S. rebaudiana* extracts. This study again suggests that these sweetener materials are safe for human consumption, and, in addition, indicates a lack of carcinogenic potential by the constituents of *S. rebaudiana* leaves.

10. Although it has been claimed in a single brief experimental paper that an aqueous extract of *Stevia rebaudiana* produced antifertility effects in male and female rats, such observations have not been confirmed in subsequent more comprehensive investigations for either male or female laboratory animals. There is also no evidence that *S. rebaudiana* extracts or their constituents produce teratogenic symptoms in rodents.

11. Several mutagenicity tests performed in a number of laboratories on *Stevia rebaudiana* extracts and constituents have all afforded negative data. However, metabolically activated steviol, the aglycone of the *S. rebaudiana* sweet constituents, has been shown by three different laboratories to be mutagenic in a forward mutation assay. Untreated steviol was not mutagenic in this manner, and the chemical nature of the active steviol metabolite(s) is not yet clear. However, these mutagenicity results might well be considered in tandem with the lack of carcinogenic effects noted as a result of the rodent chronic toxicity study on *S. rebaudiana* extracts mentioned in paragraph 9 above.

12. There have been limited *in vivo* and *in vitro* data published on the metabolism of the sweet principles of *Stevia rebaudiana*, although pure stevioside is converted to steviol and other substances in the rat. No metabolic products of the *S. rebaudiana* sweet constituents have yet been determined for humans.

13. Several meeting abstract reports from South America, few of which have been backed up by full peer-reviewed papers, have provided some evidence that extracts of *Stevia rebaudiana* and stevioside have various types of biological activity, including hypotensive and hypoglycemic effects. In addition, pure stevioside and several analogs have been found to have physiological effects in cellular and

sub-cellular metabolism. The significance of these studies on the use of *S. rebaudiana* products as sucrose substitutes is not apparent at present.

14. A compound of uncertain structure and source, "dihydroisosteviol", has been reported to have weak anti-androgenic activity in a chick-comb assay. However, this substance is not known to occur naturally, and has not been identified as a chemical degradative product of any *Stevia rebaudiana*-derived constituent.

CONCLUSION:

It may be concluded that the vast majority of the scientific safety evaluation studies which have been performed to date endorse the use of *Stevia rebaudiana* leaf and stevioside as sucrose substitutes. This is substantiated by the extensive use in Japan of these products without a single adverse report to date.

I. COMMON USE

A. Paraguay

Stevia rebaudiana (Bertoni) Bertoni, a plant native to northeastern Paraguay and southwestern Brazil, was described in separate reports by Gosling (1901)[1] and Bertoni (1905)[2] as being useful for the sweetening of bitter-tasting stimulant beverages. According to Gosling (1901), "a few leaves of this sweet herb are sufficient to sweeten a strong cup of coffee or tea, giving it also a pleasant aromatic flavour". It is indicated in several subsequent review articles or reports [3,4,5,6,7] that crushed leaves of this plant have been used by the Guarani Indians in Paraguay to sweeten the maté beverage since before their colonization by the Spaniards in the 16th century. Paraguayan Indians have also used *S. rebaudiana* leaves to sweeten alcoholic beverages and to improve the flavor of tobacco.[7] More recently, however, the practice of using *S. rebaudiana* leaves to sweeten maté and other beverages in Paraguay appears to occur only sporadically.[8]

For at least the last 45 years, *S. rebaudiana* has been prescribed by some Paraguayan physicians for the treatment of diabetes.[9] One such product (El Dulce Te del Paraguay™, L.E. de Gasperi, Asunción, Paraguay) consists of the leaves, flowers, and fine branchlets of milled *S. rebaudiana*. An initial daily dose of up to 5 g, prepared in the form of a tea, is recommended for patients with high blood sugar levels, with a maintenance dose of 1 g/day suggested for stabilized patients. Teas of the product are prepared by boiling the stipulated amount of *S. rebaudiana* powder in water, with the resultant decoction consumed either hot or cold. The tea so produced can be mixed with juices of lemon, orange, or pomelo, or can be consumed with maté. Based on an expected yield of 5-10% w/w of stevioside in the leaves of *S. rebaudiana*[4], the 5 g starting dose of the tea would

contain 0.25-0.5 g of stevioside, and the 1 g maintenance dose would represent 0.05-0.1 g of this substance. Another manner in which this product may be consumed is to produce a concentrate or "honey" by boiling 50 g of plant material with 1 liter of water until the consistency of a syrup is produced. The appropriate dose is then added dropwise to beverages such as coffee and fruit juice. While there is little basis for the efficacy for the medicinal use of *S. rebaudiana* teas in this manner (see Section II.G.3 of this report), it is significant that this prescription product is claimed to have a wide margin of safety.[4] In a recent report, it was pointed out that indigenous peoples in Paraguay have had the custom of preparing small capsules containing *S, rebaudiana* leaves to relieve physical and emotional fatigue.[7]

According to Jacobs[3], there is no evidence that people in Paraguay have ever experienced any harmful effects as a result of ingesting *S. rebaudiana* products. Furthermore, there have been no reports in the medical literature indicating any adverse effects as a result of prescribing *S. rebaudiana* teas in Paraguay.

B. Japan

1. Overall History

The introduction of *Stevia rebaudiana* as a sweetening material in Japan is attributed to Tetsuya Sumida, who observed the intensely sweet taste of this plant when he was sent by the Japanese government to the Northern Agricultural Institute in Brazil during the period 1969-1971. Sumida sent seeds of the plant from Brazil to Japan, and was then responsible for conducting cultivation experiments on the plant in various parts of Japan, including the Tokyo district and the northern island of

Hokkaido.[10] It has been reported that the plant was also imported from Paraguay in 1970 to the Cultivation Station of the National Institute of Health at Kasukabe in Japan.[11] By 1979, Japanese commercialization of *S. rebaudiana* had been very rapid, which is attributable to several facts. First, by that time, sucrose consumption was being curtailed for health reasons concerned with obesity, diabetes, and dental caries. Second, certain artificial sweeteners had been banned or severely restricted in Japan in the 1960s. Third, by the 1970s there was a perception among the Japanese public (which still persists) that synthetic chemicals are inherently more harmful than natural substances.[11] Research in Japan has led to cultivated varieties of *S. rebaudiana* that yield 3-5% more sweet diterpene glycosides than produced by wild Paraguayan specimens of the plant. The most favorable non-indigenous growing areas are warm regions in Kyushu island in Japan, as well as in other subtropical countries in eastern Asia, including Taiwan, Malaysia, and South Korea.[5] By 1988, *S. rebaudiana* products had become the most important potently sweet substances utilized in Japan, in possessing an estimated 41% of the market share worth about 3 billion yen, of a total value of 7.2 billion yen.[12] Research and development on *S. rebaudiana* sweetening products in Japan has been fostered by a group of companies that constitute the Stevia Association ("Stevia Konwakai"). In 1985, membership of this organization consisted of the following: Dainippon Ink Kagaku Kogyo Co., Ltd., Tokyo; Fuji Kagaku Co., Ltd., Toyko; Ikeda Toka Kogyo Co. Ltd., Hiroshima; Maruzen Kasai Co., Ltd., Tokyo; Morita Kagaku Kogyo Co., Ltd., Osaka; Nikken Kagaku Co, Ltd., Tokyo; Sanyo Kokusaku Pulp Co., Ltd., Tokyo; Sekisui Kagaku Kogyo Co., Ltd., Osaka; Tama Seikagaku, Co., Ltd., Tokyo; Tokiwa Seikagaku, Co., Ltd., Tokyo; Tokiwa Shokubutsu Kagaku Laboratories

Co., Ltd., Chiba; Yoto Foods Co., Ltd., Tokyo.[4] According to a recent Paraguayan report, in Japan there are now 14 companies dedicated to the processing of *S. rebaudiana*, with 40 companies involved in the elaboration of some 70 *S. rebaudiana* containing products, inclusive of canned goods, foodstuffs, pickles, sauces, and sweeteners used in the production of bakery goods, ice cream and soft drinks.[7]

2. Form in Which Used

In Japan, *Stevia rebaudiana* products are used as extracts categorized by their various concentration levels of stevioside, the major sweet glycoside constituent of the plant. For example, one company (Ikeda Toka Co., Ltd.) produces Stevia ST-AB™, which is a white powder composed of stevioside of over 90% purity, as well as Histevia-500™ and Histevia-100™, which contain stevioside in about 50% and 10% purity, respectively. The "ballast" in each case is described as "natural material", which is presumably a mixture of various non-sweet constituents of *S. rebaudiana* leaves. The same company produces a range of products (Licostevia™) in which *S. rebaudiana* extractives are combined with glycyrrhizin (another natural sweetener), sodium citrate, and "natural material".[11] Similarly, another company (Maruzen Kasei Co., Ltd.) manufactures various products in the Malmiron™ line, with up to 50% stevioside, with or without glycyrrhizin.[13] More recently, it has been practicable to manufacture pleasant-tasting *S. rebaudiana* extracts containing a high proportion of rebaudioside A relative to that of stevioside, as exemplified by the Chrysanta™ product line (Dianippon Ink & Chemicals, Inc.).[14] Four *S. rebaudiana* products, namely, Stevia extract, Stevia essence, Stevia powder and Stevia sweetener, were included in the

List of Food Additives Excluding Chemical Synthetics, published in 1989 by the Ministry of Health and Welfare, Japan.[15]

3. Categories of Foods in Which Used

A detailed analysis of the *Stevia rebaudiana*-derived sweetening products sold by Maruzen Kasei Co., Ltd. has been provided by Kazuyama.[13] This natural sweetener was utilized in the following (in decreasing order of sales volume): Japanese style pickles; dried seafoods; flavoring materials; fish meat products; vegetables and seafood boiled down with soy sauce; miscellaneous categories of use; and confectionery products. Fijita and Edahiro[11] and Kazuyama[13] have itemized *S. rebaudiana*-containing formulations for "tangles" (a type of seaweed) boiled down with soy sauce, carbonated drinks, ice cream, orange juice, and orange sherbet, in which the stevioside content was in the range 0.05-0.075% w/w or w/v. For example, in a formula for a carbonated beverage, the following ingredients were stipulated: granule sugar, 17.8 kg; Histevia-100™, 147 g; citric acid, 280 g; sodium citrate, 22 g, cider essence, 220 ml, and carbonated water to 100 liters. As this *S. rebaudiana* formulation contains 10% stevioside, the total amount of this sucrose substitute used per liter of the beverage would be 73.5 mg (0.0735% w/v). By replacing 10-20% of the sucrose in the formulation with stevioside in this manner, it was claimed that the heavy sweetness of sugar was removed, leading to more refreshing and "straightforward" drink.[11] The high-rebaudioside A-containing *S. rebaudiana* product, Chrysanta AX-P™, is recommended by its manufacturer for the replacement of 10-30% of the sucrose in cookies and drinks, and may also be employed in the formulation of candies, chewing gum, ice cakes, meat products, marine processed products, pickles

and seasonings.[14] Recent figures indicate that *S. rebaudiana* sweeteners produced by all Japanese manufacturers are used in descending order in the following categories: salty foods; drinks; "jelly" delicacies; table-top sweeteners; and other uses.[12]

S. rebaudiana extracts containing stevioside have several particular advantages as natural non-caloric sucrose substitutes for the sweetening and flavoring of foods consumed in Japan. For example, Japanese-style vegetables, dried seafoods, soy sauce, and miso (bean paste) products are usually formulated with high levels of sodium chloride, a preserving and flavoring agent, and stevioside has been found to possess a mellow taste that suppresses the pungency of sodium chloride.[13] Stevioside is relatively stable under the normally elevated temperatures involved in food processing, and does not turn brown on heating or ferment during use. The compound is also regarded as possessing preferential hedonic attributes when compared with glycyrrhizin. Unlike the latter substance, stevioside does not precipitate at the acid pH levels (*circa* pH 3) characteristic of many soft drinks.[16] The Chrysanta™ product that contains high levels of rebaudioside A has high heat stability even at low pH levels in the range 2-4, and is considered to deleteriously affect food materials in a much less substantial manner than the artificial sweetener saccharin.[14]

4. Consumption Patterns

There has been a pattern of increasing use of quantities of *Stevia rebaudiana* leaves in Japan since its introduction there in the early 1970s. Figures for 1976 indicated that of 100 metric tons (dry weight) of *S. rebaudiana* leaves used in Japan, 70% of this quantity was cultivated in

Japan, with 20% grown in Korea, and 10% elsewhere. The utilization of *S. rebaudiana* leaves reached 1,000 metric tons (1 million kg) in Japan in 1983, and in 1987, was estimated to be 1,700 tons. In recent years the vast majority (75%) of the *S. rebaudiana* leaves used in Japan for the production of stevioside has been imported from the People's Republic of China, with only about 15% of this plant being grown domestically.[12, 17] It has been calculated by Yamada and co-workers (1985) that if *S. rebaudiana* extracts represent about half the total sweeteners consumed in Japan by weight, then their average intake would be about 4 mg/kg/day of stevioside per person, assuming that *S. rebaudiana* extracts are about 200 times sweeter than sucrose, and that the average body weight of the Japanese is 50 kg.[18]

5. Absence of Adverse Reactions

Stevia rebaudiana extracts and/or stevioside have been widely used as sweetening agents in Japan over the last 15 years, with the total consumption of stevioside by the Japanese population in 1987 being 85-170 metric tons (85,000-170,000 kg) calculated on the basis of a 5-10% w/w yield of stevioside in *S. rebaudiana* plants. No adverse reactions have appeared in the scientific or medical literature during this period, and thus it may be concluded, on the basis of these observations, that these materials do not present a potential toxicity risk to humans.[4, 7, 17]

C. Other Countries

1. South Korea

Stevioside is approved for use as a food additive in South Korea and, after isolation from the leaves of *Stevia rebaudiana*, is required to be of at least 98% purity. Only one report has been encountered on the use of stevioside in South Korea, namely, an official analytical monograph, which specifies tests for permitted limits of arsenic and heavy metals and methods of detection for stevioside. The monograph lists a number of foodstuffs in which stevioside is not as yet approved for use in Korea, inclusive of bread, baby foods, and milk products.[19] In 1982 and 1983, South Korea produced 30 metric tons of *S. rebaudiana* leaves for consumption in Japan, but has not exported this commodity to Japan since then.[12] It is not clear what quantity of *S. rebaudiana* leaves is used to produce stevioside in Korea, or if the amount utilized is still produced domestically.

2. People's Republic of China

While large quantities of *Stevia rebaudiana* leaves cultivated in China are exported to Japan, the plant seems to have only a limited local use in the PRC.[20] For example, the product Tian Ye Ju Cha™ (Double Diamond brand, China Native Products and Livestock Import and Export Company, Xiamen City, PRC) consists of *S. rebaudiana* dried leaves packaged in 50 g bags, and is recommended for increasing the appetite, as a digestant, for losing weight, for keeping young, and as a sweet-tasting low caloric tea. It is sold in local marketplaces near its place of manufacture. According to the package information, purchasers are directed to prepare teas from this product using either hot or cold water.[21]

3. Brazil

Extracts of *Stevia rebaudiana* and stevioside are now approved for several dietary applications in Brazil. Initially, two products, *S. rebaudiana* tea and *S. rebaudiana* capsules (Eyra Distribuidora de Productos Alimenticios e Vegetais, Ltda.) were officially approved for sale in Brazil in 1980.[22] In 1986, stevioside, in the required absence of its hydrolytic products, steviol and isosteviol, was approved as a natural noncaloric sweetener in dietetic foods and drinks, with an acceptable daily ingestion level established at 5.5 mg/kg.[23] In January, 1988, *S. rebaudiana* extracts (purified so as to contain a minimum of 60% stevioside) and pure stevioside (free from steviol and isosteviol) were authorized for use as follows: (a) in foodstuffs and beverages to improve fragrance and flavors; (b) as sucrose substitutes in dietetic foods and beverages; (c) in chewing gums to improve flavor or as a sweetener; (d) in medicines; and (e) in oral hygiene products.[24] In April of that same year, stevioside (free from isosteviol and steviol), was approved for use in Brazil for the sweetening of soft drinks, with strict labeling requirements to be followed, and the proviso that sucrose may not be added to beverages sweetened with stevioside.[25]

An example of a new product line associated with this new legislation in Brazil are the *S. rebaudiana* tea products (Stevia Tea™) which were introduced to the Brazilian market by Ingá Stevia Agricola Ltda., Maringá, Parana, Brazil. The plant material for these products is grown locally in Brazil, and after drying, the leaves are sterilized with ethylene oxide. No artificial ingredients are added. Stevia Tea™ is available in ten different flavors, and may be prepared either as a hot or cold (iced)

beverage.[26] In addition, stevioside is now used in Brazil as a tabletop sweetener, and employed in beverages and yogurts.[27]

There has been concomitant increased scientific interest in *S. rebaudiana* in Brazil, as evidenced by the Third Brazilian Seminar on this sweet plant in 1986, wherein over 20 papers on mainly analytical and biological aspects of this plant were presented. This symposium was sponsored by the Brazilian Company of Agricultural and Livestock Research (EMBRAPA).[28]

4. United States

A recently published report indicates that *Stevia rebaudiana* has been imported from Paraguay and other countries by several U.S. companies for a number of uses, including as a table-top sweetener for beverages, for canning fruit, and for the preparation of bread, candies, and cookies. One company, Sunrider International (Torrance, California), is cited by Swientek[27] as marketing a *S. rebaudiana* preparation as a cosmetic and first-aid treatment for external use. Since as early as 1983, Sunrider has been marketing a *S. rebaudiana* product in the United States under the brand name of TruSweet Extract™, which is a thick brown liquid some 30-40 times sweeter than sucrose, recommended as a heat-stable natural sweetener "used most conveniently as a flavoring for teas and other beverages". It is claimed that the product "has been used satisfactorily in canning fruits and in the preparation of bread, cakes, and cookies".[29]

D. Evidence Demonstrating Safety Based on Common Use

Stevia rebaudiana and its extracts have a history of human consumption dating back several centuries, with widespread official use in foods and beverages in Japan for nearly 15 years, and most recently in Brazil. There have been no reports of adverse health effects resulting from such ingestion of *S. rebaudiana* or its extracts.[3, 4, 7, 17] It can thus be concluded from these observations that these materials are reasonably safe for human consumption in the quantities and forms in which they have been used in the diet thus far.

II. SCIENTIFIC STUDIES ON THE SAFETY OF EXTRACTS AND PURE COMPOUNDS FROM *STEVIA REBAUDIANA*

A. Acute Toxicity

Crude and purified extracts of *Stevia rebaudiana* have been subjected to acute toxicity tests in rats and mice, the results of which endorse the use of these materials for human consumption. The LD_{50} of an extract containing 50% stevioside was reported to be 3.4 g/kg, when administered intraperitoneally to rats.[30] *S. rebaudiana* extracts containing about 20% and about 40% stevioside (oral administration) exhibited LD_{50} values for rats of *circa* 17 g/kg and greater than 42 g/kg.[31] In a study performed in the United States, no evidence of acute toxicity was observed when separate 2 g/kg doses of the *S. rebaudiana* sweet glycoside constituents, stevioside, rebaudiosides A-C, dulcoside A, and steviolbioside were administered to mice by oral intubation. Moreover, no significant differences in body or organ weight relative to controls were evident at sacrifice two weeks after test compound administration.[32]

The results of these acute toxicity studies in rodents do not predict any potential risk for human populations by the ingestion of *S. rebaudiana* extracts and constituents.

B. Subacute Toxicity

It has been concluded by Akashi and Yokoyama[31] that laboratory chow containing up to 7.0% w/w stevioside produced no untoward toxic effects, when fed to male and female rats for nearly two months. In their study, groups of 15 male and 15 female rats were fed water extracts of *S. rebaudiana* containing stevioside levels in the feed of 0.28% (group A), 1.4% (group B), and 7.0% (group C). Body weights and food consumption were measured, and a number of hematological and biochemical tests were carried out. Each animal was sacrificed and autopsied at the end of the 50-day study, and gross observations on the major organs were made. Tissues were taken from 10 male and 10 female animals in each group for histopathological examination. Appropriate statistical analyses were carried out on all data obtained. No deaths were observed during the entire study, nor were there any unusual symptoms noted among the animals. Responses to light and sound, the appearance of the feces, the luster of the hair, and movements were all normal. There was a significant decrease in body weight in males of group C (high dose, 7.0% stevioside) beginning in the fifth week of the experiment. In contrast, there was an increase in the female body weights of group A (low dose, 0.28% stevioside), similar to the control groups. No marked differences were noted in any of the groups in terms of food consumption relative to controls. Some differences were noted in hematological parameters studied, but they were randomly arranged, and were within normal physiological limits. Any changes in the biochemical parameters measured during the study were not dose-related, and were considered to be normal. There were no significant differences in the urinanalyses relative to controls. Organ weights and gross characteristics on autopsy were considered to be normal following correlation with non-dose-related differences seen with the histological examinations of the lung, heart, liver, kidney, and bone marrow.[31]

A subacute toxicity study was carried out on rats using an aqueous extract of *S. rebaudiana* containing about 50% w/w stevioside. Two levels of extract were mixed with laboratory chow for feeding studies, allowing each animal to receive either 0.25 g or 0.5 g stevioside in 15 g of feed per day. Animals were fed the experimental diets for 56 days, and then sacrificed. Various parameters were measured during the course of the investigation, such as body weights, hematological measurements (red and white blood cell counts, hemoglobin, hematocrit), blood chemistry (total protein, albumin Â1-, Â2-, ß-, and Ó-globulin, glucose, triglycerides, total cholesterol, creatinine, urea, inorganic phosphate, glutamate- oxaloacetate transaminase, and lactic dehydrogenase), and histological examination of liver tissue. There were no abnormalities relative to controls reported that were dose-related, except for a significant decrease in serum lactic dehydrogenase levels.»

Neither of these two subacute toxicity studies would predict any potential harm on ingestion of *S. rebaudiana* extracts by humans.

C. Chronic Toxicity - Carcinogenicity

A chronic toxicity study on the ingestion of *Stevia rebaudiana* extracts has been conducted in Japan.[15] A hot-water extract of *S. rebaudiana* leaves was purified so as to contain the equivalent of about 95% total sweet glycosides (74.5% stevioside and 16.3% rebaudioside A). Male and female F344 rats were fed with laboratory chow containing either 0.1%, 0.3% or 1.0% by weight of the purified plant extract. Altogether, 480 rats (240 of each sex) were employed, and divided randomly into four groups that were comprised of control, high- and medium-dosed animals (70 males and 70 females each) and low-dosed animals (30 males and 30 females). The upper dose employed (1% of the total feed) took into account a calculated daily human intake of *S. rebaudiana* sweeteners in Japan (4 mg/kg/day), and allowed a safety factor of 100.

The duration of the investigation was 22 months for the male rats and 24 months for the females. After periods of six and 12 months, 10 males and 10 females from each group were sacrificed for clinical and histopathological examination. Individual body weights and food consumption levels were recorded at one-week intervals, with water intake measured weekly for the first 48 weeks of the study and every four weeks thereafter. Rats were checked daily, and moribund animals were sacrificed and subjected to histopathology. Urinalysis, as well as hematological, blood biochemical, and pathological examinations were performed on the control and dosed animals. Statistical methods were used to properly evaluate the test data obtained.[11]

While the growth rate of the low-dose (0.1%) group was similar to that of the controls, growth was depressed slightly after week 69 in males and after week 11 in the females in the medium-dose (0.3%) group. Transient growth retardation was observed in the high-dose (1.0%) group between weeks 23 and 50 (males) and between weeks 60 and 75 (females). After week 69 (males) and week 79 (females), the weights of the rats tended to decrease in all groups, including the controls. The general appearance and behavior of the animals were the same in all groups, including the controls. Mortality at the end of the study did not differ significantly for *S. rebaudiana*-extract treated animals when compared to the controls. After urinalysis, no dose-related changes were found, except for an increased incidence of proteinuria in females after six months. Also after this time-period, dose-related increases in erythrocyte counts and decreases in mean corpuscular volume and mean corpuscular hemoglobin were observed in male rats, with decreased erythrocyte counts in female rats. However, the differences between the hematological parameters of the dosed and control rats after 12 months were not statistically significant. Administration of the *S. rebaudiana* extracts for six months caused a increase in blood glucose for animals of both sexes, and decreases of blood glutamate-oxalacetate transferase, glutamate-pyruvate transaminase,

and triglycerides in females. No significant differences in blood biochemical values occurred between any of the four groups of animals either after 12 months or at the end of the experiment. Organ weights of the liver, kidneys, heart, prostate, and testes were significantly increased in males relative to controls in the high-dose group after six months. Analogous (six-month) data obtained for females in the high-dose group indicated significant decreases in ovary weights and increase in liver weights. Again, changes in organ weights for all dosed animals employed in the study were not significantly different from controls after 12 months or at the end of the study.[11]

A variety of non-neoplastic histopathological findings were recorded, and, in most cases, both animals dosed with *S. rebaudiana* extracts and control animals exhibited similar conditions. Changes more common in rats given *S. rebaudiana* extracts than in control animals were reduced spermatogenesis, interstitial cell proliferation in the testes, medullary cell proliferation in the adrenal glands, atrophy of the thymus, inflammatory lesions in the trachea and lungs, age-related changes of the kidneys, such as degeneration of tubular epithelium, hyaline casts, and glomerular sclerosis, and pigmentation and increased hematogenesis of the spleen. A number of neoplasms were observed, both for the control and *S. rebaudiana*-dosed animals. The most common neoplasms in the males were interstitial cell adenoma of the testes and pheochromocytoma of the adrenal glands, while in the females they were interstitial polyps of the endometrium and adenoma of the anterior lobe of the pituitary. The incidence of neoplasms was not related to dose.[11]

As a result of this protracted and extensive investigation, it was concluded that no significant dose-related changes were found in the growth, general appearance, hematological and blood biochemical findings, organ weights, and macroscopic or microscopic observations, as a result of feeding male and female F344 rats with *S. rebaudiana* extracts at levels up to 1% of their feed for about two years. It was also

concluded that any neoplasms that occurred were not attributable to the administration of *S. rebaudiana* extracts.[11]

This is the most extensive safety study performed to date on *S. rebaudiana* extracts, involving nearly 500 test animals that were treated for up to two years. The highest dose level administered to the animals represented some 100 times the estimated daily intake of this sweet material in the human diet. The results obtained are supportive of the safety of *S. rebaudiana* extracts, stevioside and rebaudioside A when consumed as sucrose substitutes by human populations.

D. Effects on Reproduction

It was claimed in 1968 by Planas and Kuc that the Paraguayan Matto Grosso Indians have employed the leaves and stems of *Stevia rebaudiana* in the form of a tea as a contraceptive. These workers also reported an antifertility effect for periods up to two months following the incorporation of a 5% *S. rebaudiana* extract (10 ml) into the drinking water of both male and female rats.[9]

Recent field inquiries in various regions of northeastern Paraguay, however, do not confirm the native use of *S. rebaudiana* extracts for contraceptive purposes.[7] Moreover, a number of other laboratories have been unable to confirm an antifertility activity of *S. rebaudiana* extracts in rats.[4] In one such laboratory study conducted in Japan, an extract of *S. rebaudiana* leaves containing 53.1% stevioside was mixed with standard laboratory ration to afford various dose levels of stevioside for feeding to groups of rats. After receiving normal ration for several days, 13-week-old male and female SLC-Wistar strain rats were fed a stevioside-containing ration for 21 days. After this period, one male was placed with two females for mating. Female rats were examined daily for evidence of a vaginal plug, and this day was considered as day 0 of pregnancy. On day 20, half the pregnant animals were laparotomized and the

remaining half were allowed to have spontaneous deliveries. At the time of mating, the stevioside-containing rations were removed and substituted with standard laboratory diet. The data obtained showed a lack of antifertility effects for the extracts tested. Furthermore, there was no evidence of any teratogenic activities or other abnormalities in the fetuses or offspring.[33]

In a later study, it was reported that male and female rats, maintained with up to 3% stevioside in the diet, exhibited no abnormal signs in mating performance and fertility. Also, no skeletal or other teratogenic effects attributable to stevioside were observed in fetuses after birth.[33]

A recent chronic feeding study, carried out in Brazil using an aqueous extract of *S. rebaudiana* leaves, has investigated the endocrine parameters of male rats thus treated. The pre-pubescent (immature) test animals were dosed twice daily for 60 days with plant extract (2 ml of a solution represented by 66.7 g of dried leaves per 100 ml total solution). A number of measurements were made (glycemia; serum levels of T_3 and T_4; available binding sites in thyroid-hormone-binding proteins (T3R index); binding of [3H]R1881 to prostate cytisol; zinc content in prostate, testis, submandibular salivary gland and pancreas; water content in testis and prostate; body weight gain, final weights of testis, prostate, seminal vesicle, submandibular salivary gland, and adrenal). The group treated with *S. rebaudiana* did not differ significantly from the control group with respect to all parameters measured, with the exception of seminal vesicle weight, which fell by 60%. It was concluded that the administration of *S. rebaudiana* aqueous extract produced no diminution of fertility in male rats.[34]

A similar study carried out in France has shown a lack of any anti-androgenic activity of extracts of *S. rebaudiana*. Groups of five adult male Wistar rats were given orally (for each of 31 days) either a control or one of three test solutions containing an

aqueous extract prepared from 0.5 kg of *S. rebaudiana* leaves (calculated to contain 2.6% w/w stevioside before dilution). After autopsy, the testicles, prostate gland, and seminal vesicles of the treated rats were weighed and compared with control values. Since no significant differences were observed, it was concluded that no anti-androgenic effects by *S. rebaudiana* were apparent.[33]

Therefore, all scientific studies subsequent to the Planas and Kuc paper of 1968 have refuted these initial observations of an antifertility affect of *S. rebaudiana* leaves on male and female rats.

E. Mutagenicity Potential

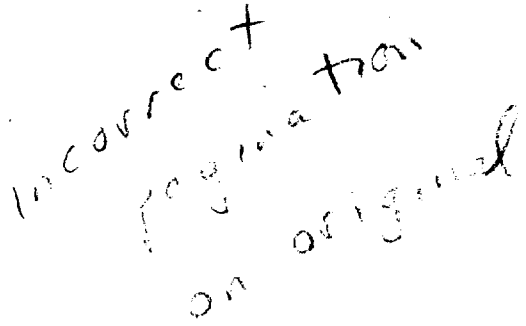
Partially purified extracts and pure compounds (stevioside, rebaudiosides A-E, dulcoside A, and steviolbioside) from *Stevia rebaudiana* leaves have been extensively tested for their mutagenic activity. Utilizing *Salmonella typhimurium* strains TA98, TA100, TA1538, and TM677, or *Escherichia coli* strain WP2, either in the presence of absence of a 9,000 x g supernatant metabolic activating system derived from the rat liver (S-9), all of these materials have been reported as nonmutagenic in laboratories in Japan, Brazil, and the United States.[36,37,38,39,40] Mutagenicity tests performed with recombination deficient (rec-) strains of *Bacillus subtilis* (H17 and M45) have also shown several of these substances to be innocuous, both in the presence and absence of S-9, as have host-mediated tests in mice bearing *S. typhimurium* strain G46.[36]

However, recent studies in the United States, Japan and the United Kingdom, have shown that steviol, the aglycone of *S. rebaudiana* sweet constituents such as stevioside and rebaudioside A, is mutagenic in a forward mutation assay utilizing *S. typhimurium* strain TM677 in the presence of a metabolic activating system, derived from a 9,000 x g supernatant fraction obtained from the livers of Aroclor-1254 pretreated rats. Unmetabolized steviol is inactive in this system.[38,39,40] Furthermore,

metabolically activated steviol also gave positive responses in chromosomal aberration and gene mutation tests carried out in Japan.[39] In contrast, however, the Japanese study demonstrated that activated steviol was not mutagenic in the reverse mutation assay (Ames test) using *S. typhimurium* strains TA97, TA98, TA100 and TA102.[39]

Several steviol analogs have also been assessed for mutagenicity under the same conditions used for steviol, so that a preliminary notion of structural requirements necessary for the exhibition of a mutagenic response among this class of compounds might be established. As a result of its generation under the conditions used to produce a bacterial mutagenic effect by steviol, 15Â-hydroxysteviol has been shown to be a major metabolite of steviol. While this compound was not mutagenic, its closely related derivative, 15-oxosteviol, was found to be a direct-acting (albeit very weak) mutagen in the *S. typhimurium* TA677 forward mutation assay. 15-Oxosteviol, however, has not been detected among the products of steviol metabolism, and it still remains to be shown that this compound can be enzymatically generated from either steviol or 15Â-hydroxysteviol. Conversely, it is possible that other undefined mutagenic metabolites may be generated from steviol under the experimental conditions used.[41,42] It should be pointed out that scientists in the United Kingdom recently failed to reproduce a direct mutagenic response for 15-oxosteviol, when studied in the *S. typhimurium* TM677 forward mutation assay, and have therefore challenged the earlier assertion that this compound is a weak direct-acting mutagen.[40]

As discussed in section II.F below, steviol is a metabolite of both stevioside and rebaudioside A in rats. Thus far, however, there is no evidence that *S. rebaudiana* extracts containing stevioside are biotransformed to steviol by ingestion by humans, although this cannot be ruled out at this stage. Even if this were found to occur, steviol itself has not been found to be mutagenic, and would require further transformation in the body to elicit a mutagenic substance or substances. In addition, by no means are all



"proven" mutagens carcinogenic, and several dietary chemicals are known mutagens. For example, when nearly 250 synthetic and naturally occurring food additives were subjected to testing in a reverse mutation assay using various *Salmonella typhimurium* strains (Ames test), 14 such compounds were positive in this test. This study was carried out on substances with well-established food use in Japan, by the National Institute of Hygienic Sciences, Tokyo, Japan.[43] Also, the results of these mutagenicity experiments on steviol are perhaps of less significance that those of the chronic toxicity studies mentioned in section II.C of this review, wherein no significant incidence of tumor formation was reported in rats dosed for about two years with

S. rebaudiana extracts (up to 1% of total diet), when compared with control animals.

F. Metabolism Studies

There are only somewhat limited data on the *in vivo* and *in vitro* metabolism of the sweet principles of *Stevia rebaudiana*, such as stevioside. In 1980, Wingard and co-workers demonstrated that stevioside and rebaudioside A are both degraded to steviol by rat intestinal microflora *in vitro*. In the case of stevioside, incubation with bacterial cecal suspensions under the conditions used in the experiment for two days resulted in 100% conversion to steviol, with 100% conversion of rebaudioside A to steviol occurring only after six days. Steviol was detected by high-performance liquid chromatography, and, when subjected to the same type of incubation, was recovered unchanged in 87-100% yield after two-six days. Cell-free extracts transformed stevioside and rebaudioside A more slowly, with 50% and 7% conversion to steviol of stevioside and rebaudioside A, respectively, occurring after seven days' incubation. Wingard and co-workers (1980)[44] extrapolated their rat data to the human situation, and have suggested that the human bowel could convert over 0.4 g rebaudioside A to steviol each hour. However, this calculation may be somewhat presumptuous because humans do not have a functional cecum and therefore contain different intestinal-tract microbial flora than the rat.[4]

A more recent investigation by Nakayama and colleagues (1986)[45] has studied the *in vivo* absorption, distribution, metabolism and excretion of pure stevioside in Wistar rats. Tritiated stevioside was administered orally at a dose of 125 mg/kg, and the level of radioactivity in the blood increased slowly to a maximum of 4.83 mg/ml at eight hours, indicating a biological half-life of 24 hours.

After one hour, the highest concentration was in the small intestine, followed, in turn, by the stomach and cecum. After four hours, the concentration in the cecum was higher than in other organs, and after 120 hours, the percentages of radioactivity excreted into the feces, expired air, and urine were 68.4%, 23.9%, and 2.3%, respectively. Some evidence was obtained for the occurrence of enterohepatic circulation in the rat. Steviol was found to be a major metabolite in the feces, and small amounts of stevioside, steviolbioside, and an unidentified metabolite were also found. It was inferred that while a portion of orally administered stevioside is excreted in the feces, most of it is degraded by the rat intestinal bacterial flora to steviolbioside, steviol, and glucose, which are then absorbed. Absorbed glucose is considered to be metabolized and excreted in expired air as carbon dioxide and water, with most of the steviol conjugated in the liver and excreted into the intestinal tract via the bile. Free steviol may be reformed by decomposition of the its conjugated form by intestinal bacteria).

It still remains to be shown that *S. rebaudiana* sweet constituents such as stevioside and rebaudioside A are metabolized in humans in the manner described in the studies by Wingard et al.[44] and Nakayama et al.[45].

G. Other Biological Investigations

1. Cardiovascular Effects

Several reports based on work carried out in Brazil have described various cardiovascular effects of *Stevia rebaudiana* extracts. Thus, when a tea prepared from *S. rebaudiana* leaves (50 g) was administered daily for 30 days to 18 normal human subjects, ranging in age from 20-40 years, a *circa* 9.5% lowering of the systolic and diastolic blood pressure resulted. There was a prolongation noted in the electric systole in the ECG. When a

single oral dose of *S. rebaudiana* tea prepared from 3.0 g of leaves was given to 10 normal adult human subjects, only a slight lowering of only the systolic blood pressure was noted.[46] When two concentrations (8 and 16 mg/kg) of pure stevioside were tested by Melis and Sarnati (1991)[47] on normal male Wistar rats, it was concluded that this substance produced dose-dependent hypotensive activity. Animals were subjected to tracheostomy, with the left carotid artery catheterized, and isotonic Ringer solution containing 10% inulin and 2% *para*-aminohippuric acid infused i.v. at the rate of 0.03 ml/min throughout the experiment. Four groups of clearance studies were performed: (a) stevioside dissolved in isotonic saline infused at a priming dose of 8 mg/kg and then at a rate of 8 mg/kg/hr; (b) stevioside used in the same manner as in (a), except at higher dose (16 mg/kg); (c) and (d) control groups using verapamil and calcium chloride. The stevioside dose at 16 mg/kg produced a significant increase in *para*-aminohippuric acid clearance, although this effect was not observed at the lower stevioside dose (8 mg/kg). It was put forth as a result of this study that the vasodilator effect of stevioside induced a decrease in mean articular pressure and promoted renal vasodilation by lowering renal vascular resistance. The authors made no attempt to speculate on how the results of this investigation might impact on the use of *S. rebaudiana* extracts and stevioside as sweetening agents.

At the Third Brazilian Seminar mentioned in section I.C.3 of this review[28], an abstract of a clinical study appeared in the proceedings, describing the effects of the administration of a lyophilized *S. rebaudiana* extract on the cardio-circulatory and electrolytic profiles of 60 healthy human subjects.[48] The participants were split into three groups, and

received capsules containing the equivalent of 0 mg (placebo), 27.7 mg, or 110.8 mg stevioside. It was observed that with the higher dose, there was a tendency for the lowering of both systolic and diastolic arterial pressure, as well as a trend towards a reduction of glycemia. However, the administration of the capsules caused no perceptible undesirable effects in any of the subjects, and did not cause any significant changes in over 20 standard blood chemical measurements. It was concluded that the acute use of *S. rebaudiana* did not lead to any significant alteration of homeostasis or organ function.[48] No full research report appears to have appeared in the literature in relation to this study.

Although it would seem that stevioside would not cause hypotensive effects at the doses used in sweetening foods and beverages, definitive clinical studies to clarify this point are needed.

2. Allergenicity

No published reports have appeared that would suggest that extracts of *Stevia rebaudiana* leaves are immunologically active when taken internally. Similarly, there is no evidence that any of the constituents of *S. rebaudiana* cause allergic contact dermatitis.

3. Effects on Carbohydrate Metabolism

In section I.A of this review, the use was described of teas prepared from *Stevia rebaudiana* leaves as a diabetes remedy in Paraguay. Hypoglycemic effects in humans and rats using *S. rebaudiana* extracts have been documented in a number of scientific publications[49,50,51,52,53,54], thus providing some credence for this medicinal use of the plant in Paraguay.

In a preliminary study using human subjects in 1970, Oviedo and co-workers administered a dried aqueous extract of *S. rebaudiana* leaves orally to each of 25 healthy adults (dose not specified), in a "double-blind" study. They claimed an average 35.2% fall in normal blood sugar levels from initial values, between six and eight hours after administering the extracts.[49] In a Brazilian study, daily administration of an aqueous *S. rebaudiana* extract (equivalent to 1 g stevioside) was provided to each of 15 normal humans subjects (both male and female, 19-25 years-of-age). The extract was given in 250 mg stevioside-equivalent doses every six hours, and the first dose was given 12 hours after a glucose tolerance test, with the last dose two hours before a second glucose tolerance test four days later. The results showed an "accentuated hypoglycemic response" in the patients studied, but it is not clear if any controls were included in this investigation.[50] In a laboratory study conducted on rats, a high-carbohydrate diet containing 10% dried *S. rebaudiana* leaves (corresponding to about 0.5% stevioside) was studied. After two weeks of feeding, there was a significant decrease in liver glycogen, which further decreased after four weeks of feeding. Blood glucose was unaffected after two weeks of feeding, but was significantly decreased at four weeks, when compared with control values.[50]

The influence of stevioside on the transport and metabolism of D-glucose and D-fructose was investigated in the isolated perfused rat liver by Ishii and co-workers (1987).[52] Stevioside was found to be without effect on D-glucose metabolism, except for transient changes in the release of this compound, although D-fructose was specifically affected. According to the

investigators, their results are compatible with previous observations[50,51] of the effects of *S. rebaudiana* constituents on carbohydrate metabolism.

However, despite the above-mentioned studies, the effects of *S. rebaudiana* constituents on carbohydrate metabolism are contradictory, since a number of other laboratory investigations have found no significant effects of this type. For example, Lee and co-workers (1979)[30] found no change in blood glucose levels, when crude extracts of *S. rebaudiana* leaves were fed to rats for 56 days, with each rat consuming from 0.5-1 g of extract per day. Akashi and Yokoyama (1975)[31] found no dose-related effects on blood glucose after feeding studies in rats for 50 days using extracts of *S. rebaudiana* in which the final concentration in the ration was 7.0%. In more recent work, Medon and Zeigler (1986)[53] treated male Sprague-Dawley rats (68-146 g) with pure stevioside (orally, 75-150 mg/kg) for period of up to 30 days. Blood samples were collected via the tail vein either 0, four, eight and 24 hours (acute study) or one, two, three, and four weeks (chronic study) following compound administration. Plasma glucose levels were determined using a glucose analyzer. Acute or chronic administration of stevioside produced no significant differences to controls in blood glucose of rats. It was concluded that the data obtained did not support a hypoglycemic activity of stevioside.

Therefore, the effects of *S. rebaudiana* extracts and constituents on carbohydrate metabolism are conflictory in scientific studies to date, and should be clarified further.

4. Effects on Cellular and Sub-Cellular Metabolism

A series of studies on the effects of pure stevioside and several glycosidic and non-glycosidic derivatives have been performed and reviewed by Brazilian workers.[54] The activities of these compounds have been probed in systems such as isolated rat liver mitochondria, rat renal cortical tubules, human and rabbit erythrocytes, rabbit reticulocytes, and in the isolated, perfused rat liver. In general, *S. rebaudiana* glycoside constituents such as stevioside and steviolbioside were found not to affect mitochondrial functions, although the non-glycosidic substances, steviol and isosteviol, which do not occur naturally, were active in this regard.

5. Anti-Androgenic Effects of Steviol and "Dihydroisosteviol"

Steviol, the enzymatically produced aglycone of the *Stevia rebaudiana* constituent, stevioside, has been studied in a chick-comb assay, which involved inunction of the compound to the combs of two-day-old white leghorn male chicks stimulated by a single injection of testosterone.[55] Steviol was given once daily for seven days, and then the combs were removed and weighed. Doses of steviol used in three separate experiments were 0.5, 2.0 and 3.0 mg/comb (total given to each chick in a seven-day treatment period). The results at the 0.5 mg/comb level were negative, but for the 2.0- and 3.0-mg/comb doses a "tendency toward anti-androgen activity was observed". A compound of apparently unknown structure that was referred to as "dihydroisosteviol" was tested in this chick-comb assay in a similar manner. It showed a statistically significant anti-androgen effect only at the 3.0 mg/comb level. In 28-day-old Charles River male castrated rats, "dihydroisosteviol" did not affect the seminal vesicles, prostate, or

levator ani, and was not effective in inhibiting the action of testosterone given at total subcutaneous dose levels of 5.0 and 20 mg per animal. Injections of the test compound were given in divided doses daily for seven days.[55] It may be pointed out that "dihydroisosteviol" has never been determined as a metabolic or degradative product of any of the *S. rebaudiana* diterpene glycoside sweeteners. The origin of "dihydroisosteviol" was not stated.

H. Evidence of Safety Based on Scientific Studies

As discussed above, scientific studies have been carried out in several major safety categories, including acute toxicity[30,31,32], subacute toxicity[29,30], chronic toxicity[18], and effects on reproduction.[30,33,34,35] These studies have shown no dose-related abnormalities that are significant from a safety stand-point, and thus are supportive of the safety of *S. rebaudiana* extracts for human consumption in the quantities and forms in which they have been used in foods and beverages.

III. BOTANICAL, CHEMICAL AND MISCELLANEOUS TECHNICAL DATA

A. Identity

1. Botanical Description of *Stevia rebaudiana*

The genus *Stevia* belongs to the family Compositae (Asteraceae), in the tribe Eupatoriae, and is an entirely New World genus, with a distribution ranging from the southern United States to northern Argentina, through Mexico, Central America, the South American Andes, and the Brazilian highlands. The number of species has been placed in the range of 150-300, of which 80 species are known to occur in North

America, with at least 70 species being indigenous to Mexico alone. Members of the genus comprise herbs (annuals and perennials) and shrubs, found mostly at altitudes of 500-3,000 meters above sea level. Although they are usually found growing in semi-dry mountainous terrains, habitats of *Stevia* species range from grasslands, scrub forests, forested mountain slopes and conifer forests, to subalpine areas.[8]

Stevia rebaudiana (Bertoni) Bertoni is a shrub native to elevated terrain in the Amambay area of northeastern Paraguay and the Iguaçu district of southeastern Brazil, and has the following botanical characteristics:

> "Suffruticose, erect obscurely puberulent, 3-4.5 dm high; leaves opposite, sessile, lance-oblong to spatulate-oblanceolate, obtuse, serrate above the middle, entire on the cuneately narrowed basem of chartaceous or subcoriaceous texture, 3-nerved and conspicuously veiny, the cauline 3-5 cm long, 7-15 mm wide, often proliferous in the axils; inflorescence becoming rather loosely paniculate, the heads (on pedicels often about as long as the involucre) appearing opposite the bracts in irregular sympodial cymes,; corollas with pale purple throat and white limb; achenes nearly uniform, 15-176 aristate".[56]

S. rebaudiana is known in the Guarani language in Paraguay as Caá-êhé, which means "sweet herb". This taxon was originally named *Eupatorium rebaudianum* Bertoni, but was later assigned to the genus *Stevia*. The correct name for this plant is *Stevia rebaudiana* (Bertoni) Bertoni rather than *Stevia rebaudiana* (Bertoni) Hemsley, for reasons of priority.[4]

2. Chemical Constituents of *Stevia rebaudiana*

While chemical work to determine the structural nature of the sweet principle or principles of *Stevia rebaudiana* leaves began at the turn of the century[3,4,5,6,7], the structure of stevioside, the most abundant sweet constituent, was not completed until more than 60 years later. A group at the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland, was able to show that one sugar unit of stevioside occurs as a glucopyranose function attached ß to a carboxyl group, and a second sugar unit occurred as a sophorose unit affixed ß to an alcoholic group of the aglycone.[57,58] The structure and stereochemistry of steviol (*ent*-13-hydroxykaur-16-en-19-oic acid), the aglycone obtained on the enzymatic hydrolysis of stevioside, were finally determined in 1963.[59] During the 1970s additional sweet compounds were structurally characterized from *S. rebaudiana* leaves, including rebaudioside A, which is sweeter than stevioside, and has a more pleasant taste.[60] The sweet *ent*-kaurenoid glycosides occur in extremely high yields in dried *S. rebaudiana* leaves, with approximate values for the four most abundant compounds being: stevioside (5-10% w/w), rebaudioside A (2-4% w/w), rebaudioside C (1-2% w/w), and dulcoside A (0.4-0.7% w/w).[4]

The structures of the eight known sweet constituents of *S. rebaudiana* are shown in Appendix I (stevioside, **1**; steviolbioside, **2**; rebaudioside A, **3**; rebaudioside B, **4**; rebaudioside C, **5**, rebaudioside D, **6**; rebaudioside E, **7**; dulcoside A, **8**). These compounds have all been thoroughly characterized by standard physico-chemical techniques such as melting point determination, optical rotation, ultraviolet spectroscopy, infrared spectroscopy, proton- and carbon nuclear magnetic resonance

spectroscopy, and mass spectrometry.[4,5,6] Thus, for example, stevioside (*Chemical Abstracts* Registry Number **57817-89-7**) exhibits: mp 196-198°C, $[]_D^{20}$ -43.2°; $C_{38}H_{60}O_{18}$, and rebaudioside A (*Chemical Abstracts* Registry Number, **58543-16-1**), mp 237-239°C; $[]_D^{20}$ -18.5°; $C_{44}H_{70}O_{23}$. Abstracts of many patented procedures for the extraction and purification of the *S. rebaudiana* sweeteners have appeared in *Chemical Abstracts* since 1973.[4,5]

Several non-sweet secondary metabolite constituents have been identified in extracts of *S. rebaudiana* leaves, including labdane diterpenes[4,61,62], triterpenes[4], sterols[4,63], flavonoids[4,64], and volatile oil constituents.[4] In addition, the pigments, gums, and inorganic matter present in the leaves of *S. rebaudiana* have been investigated.[65] The dried leaves of *S. rebaudiana* contain about 42% w/w of water-soluble substances.[3]

B. Analytical Methods for the *Stevia rebaudiana* Sweet Glycosides

There is a plethora of published analytical methods for the determination of the *Stevia rebaudiana* glycosides in plant material and food and beverage compositions. Five major methods have been used for the qualitative and quantitative analysis of these compounds, namely, gas-liquid chromatography (GLC); thin-layer chromatography (TLC)-densitmetry; colorimetric determinations; high-performance liquid chromatography (HPLC); and an enzymatic procedure.[4] A short review has appeared in the literature on analytical methods.[66]

Tezuka and co-workers (1980)[67] have published a GLC method for the determination of stevioside in sugarless chewing gum. Stevioside was analyzed in the form of isosteviol methyl ester, after hydrolysis with mineral acid 6 N sulfuric

acid, and methylation with diazomethane. Salient conditions of gas chromatography were: glass column, 30 cm X 3 mm; stationary phase, Diasolid ZT on Chromosorb W (acid washed); column temperature, program from 100C through 300C at 5C/min; carrier gas flow rate, 40 ml/min; internal standard, squalene. The method was suitable for the analysis of stevioside in chewing gum at levels of between 0.03-0.20% w/w.

Methods for the *S. rebaudiana* sweet glycosides using HPLC are preferable over other analytical procedures because they permit the compounds to be detected in their unmodified form, and also allow the simultaneous determination of several of these compounds. Makapugay et al. (1984)[68] were able to separate an artificial mixture of all eight sweet diterpene glycosides constituents of *S. rebaudiana* leaves using a gradient elution HPLC procedure. Details of this separation are: column, Zorbax NH_2, 25 cm x 04 mm; eluting solvent, 84-70% v/v acetonitrile-water (pH 5), changed over a period of 15 min; flow rate, 2 ml/min; UV detector wavelength, 210 nm; temperature, ambient. This method was applicable to the estimation of stevioside, rebaudioside A, rebaudioside C, and dulcoside A, the four most abundant sweet *ent*-kaurene glycosides occurring in *S. rebaudiana* leaves of different geographical origin. Prior to analysis, powdered *S. rebaudiana* leaves were extracted with methanol, with aliquots of each methanolic extract passed through a prepared Permaphase ETH pre-column prior to HPLC analysis. The highest % w/w dry weight values recorded for the test compounds were evident in a *S. rebaudiana* leaf sample cultivated in Taiwan, namely, stevioside, 8.1; rebaudioside 3.5, rebaudioside C, 1.4, and dulcoside A 0.53.

Similar HPLC methodology has recently been developed that is suitable for the simultaneous determination of stevioside, rebaudioside A, rebaudioside C, and dulcoside A occurring in Japanese beverage, soy sauce, candy, and pickled

radish products. The conditions employed were: column, LiChrosorb NH_2 (5 mm, 25 cm x 4 mm); mobile phase, acetonitrile-water (80:20); flow rate 0.8 ml/min; UV detector wavelength 210 nm; temperature, 50C. All types of sample were passed through a Sep-Pak C_{18} cartridge prior to being subjected to HPLC. Recoveries of the sweeteners fortified with standards at 20 and 100 ppm were in the ranges of 87.9-99.7% and 93.2-97.8%, respectively, and the limit of detection of these sweeteners in food was 5 ppm.[69]

C. Sensory Properties of the *Stevia rebaudiana* Sweet Glycosides

Stevioside, when almost pure (93-95%), exhibits a persistent aftertaste, with bitterness and astringency experienced by human volunteer subjects. However, when the compound is only 50% pure, as in certain extracts of *Stevia rebaudiana* leaves, a much less undesirable aftertaste is perceived. Using an incomplete-paired comparison organoleptic human taste panel, the sweetness of pure stevioside was found to be about 300 times that of sucrose at 0.4% sucrose concentration, 150 times sweeter at 4% sucrose concentration, and 100 times sweeter at 10% sucrose concentration.[70]

The relative intensities of sweetness for the *S. rebaudiana* sweet glycosides have been well documented (sucrose = 1): stevioside, 150-300, steviolbioside, 100-125; rebaudioside A, 250-400; rebaudioside B, 300-350; rebaudioside C, 50-120; rebaudioside D, 250-450; rebaudioside E, 150-300; dulcoside A, 50-120.[6] The range of figures in each case reflects differences in sweetener concentrations and differences in methods of laboratory assessment of sweetness.

There have been many attempts to improve the unpleasant aftertaste of stevioside, such as by formulation with either sucrose, fructose, glucose, amino

acids and cyclodextrins. Most of these methods have appeared in the Japanese patent literature.[4,5]

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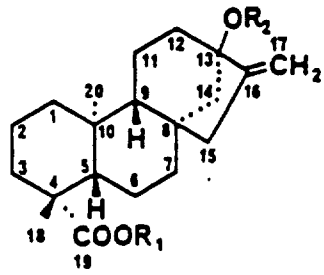
APPENDIX I

Structures of the Eight Known Sweet Diterpene Glycosides from *Stevia rebaudiana*



	R_1	R_2
1	β - Glu	β-Glu-β-Glu (2→1)
2	- H	β-Glu-β-Glu (2→1)
3	β - Glu	β-Glu-β-Glu (2→1) | β-Glu (3→1)
4	- H	β-Glu-β-Glu (2→1) | β-Glu (3→1)
5	β - Glu	β-Glu-α-Rha (2→1) | β-Glu (3→1)
6	(2→1) β-Glu-β-Glu	β-Glu-β-Glu (2→1) | β-Glu (3→1)
7	(2→1) β-Glu-β-Glu	β-Glu-β-Glu (2→1)
8	β - Glu	β-Glu-α-Rha (2→1)

Glu = D-glucopyranosyl; rha = L-rhamnopyranosyl

APPENDIX II.

Comments of Reviewers

UNIVERSITY OF THE PACIFIC

School of Pharmacy

Physiology and Pharmacology Department

26 March 1992

Herb Research Foundation
1007 Pearl St. (#200F)
Boulder CO 80302

Sirs:

I have studied the revised and final draft of the food safety review for Stevia rebaudiana leaves. This revision has been nicely done and constitutes a comprehensive statement on the plant in question.

I fully agree with the author's 14 summary points (pp. 2-5) and his final conclusions (p. 5) that Stevia rebaudiana leaves, leaf preparations and pure sweetening principles are all safe in the amounts now used commercially to flavor foods, drinks, etc. It is very doubtful that these plant materials would ever be used in excess of these amounts because of taste esthetics. Therefore, these materials must be considered as very safe when used as food/drink additives.

Signed:

Marvin H. Malone, PhD

3601 Pacific Avenue, Stockton, California 95211 • (209) 946-2487

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January 30, 1992

Margaret Blank
Herb Research Foundation
1007 Pearl Street, Suite 200
Boulder, Colorado 30302

Dear Ms. Blank:

I have reviewed Dr. Kinghorn's report on the safety of *Stevia* and I find this to be a truly excellent and professional article by a well-regarded expert in the area. The review is nicely arranged and appropriately critical, and I appreciated the clear statement of summary and conclusions at the beginning.

Certainly, on the basis of the evidence marshalled and reviewed in this article, there seems little scientific reason for the FDA not to approve the use of *Stevia* extracts in the United States.

Sincerely,

3601 Pacific Avenue, Stockton, California 95211 • (209) 946-2487

APPENDIX III.

Credentials of Researcher

Alan Douglas Kinghorn - Curriculum Vitae

HOME ADDRESS:

155 N. Harbor Dr., #3207
Chicago, IL 60601
(tel. 312-819-1101)

OFFICE ADDRESS:

Department of Medicinal Chemistry
and Pharmacognosy; Program for
Collaborative Research in the
Pharmaceutical Sciences
College of Pharmacy
University of Illinois at Chicago
833 S. Wood Street, Chicago, IL 60612
(tel. 312-996-0914; fax 312-996-7107)

PERSONAL DATA:

Date of Birth:	August 31, 1947
Place of Birth:	Newcastle-upon-Tyne, U.K.
Marital Status:	Married, HelenMaria
Children:	None
Social Security Number:	425-25-4779
Residential Status:	U.K. citizen; U.S. permanent resident

EDUCATION/DEGREES

Secondary - Royal Grammar School, Newcastle-upon-Tyne, U.K. (1959-1966)
College -

University of Bradford, Bradford, U.K.	B.Pharm. (Special) (Pharmacy) 1969
University of Strathclyde, Glasgow, U.K.	M.Sc. (Forensic Science) 1970
University of London, London, U.K.	Ph.D. (Pharmacognosy) 1975
University of London, London, U.K.	D.Sc. (Pharmacy) 1990

EMPLOYMENT HISTORY:

1986-	Professor	Department of Medicinal Chemistry and Pharmacognosy; Program for Collaborative Research in the Pharmaceutical Sciences College of Pharmacy University of Illinois at Chicago Chicago, IL 60612
1990	Gastprofessor (Sabbatical, April-August)	Department of Pharmacy, Swiss Federal Institute of Technology (ETH) Zurich, Switzerland
1981-1986	Associate Professor	Department of Pharmacognosy and Pharmacology, (1981-1982); Department of Medicinal Chemistry and Pharmacognosy (1982-1986), University of Illinois at Chicago, Chicago, IL 60612

February, 1992

1977-1981	Assistant Professor	Department of Pharmacognosy and Pharmacology, University of Illinois at the Medical Center Chicago, IL 60612
1976-1977	Research Associate	Department of Pharmacognosy and Pharmacology, University of Illinois at the Medical Center Chicago, IL 60612
1975-1976	Post-Doctoral Research Associate	Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677
1971-1975	Teaching Fellow (= Instructor)	School of Pharmacy, University of London, Brunswick Square, London, U.K.
1970-1971	Analytical Chemist	Burrough's Wellcome Company Ltd. Dartford, Kent, U.K.

HONORS AND AWARDS:

Open Postgraduate Studentship, University of Strathclyde, Glasgow, U.K., October, 1969-September, 1970.
Teaching Fellowship, School of Pharmacy, University of London, October, 1971-August, 1975.
Elected Fellow of the Linnean Society of London (FLS), February, 1985.
President, American Society of Pharmacognosy, 1990-1991.
President, Society for Economic Botany, 1991-1992.
Listed in American Men and Women of Science, 17th edition, 1990.
Awarded D.Sc. degree in the field of Pharmacy from the University of London, December, 1990.
Designated Fellow, Royal Pharmaceutical Society of Great Britain (FRPharmS), December, 1991.

ORGANIZATIONS:

American Chemical Society; American Society of Pharmacognosy; Convocation, University of London; Linnean Society of London (FLS); Old Novocastrian's Association; Royal Pharmaceutical Society of Great Britain (FRPharmS; registered pharmacist, No. 65192); Rho Chi (Honor Society); Sigma Xi (Honorary Research Society); Society for Economic Botany.

TEACHING EXPERIENCE:

Undergraduate -	1971-1975	School of Pharmacy, University of London (Pharmacognosy)
	1976-1984	College of Pharmacy, University of Illinois at Chicago (Pharmacognosy)

	1990	Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland (Pharmacognosy)
Professional -	1985-1992	College of Pharmacy, University of Illinois at Chicago (Chemical Aspects of Drug Action I and II)
Graduate -	1976-1992	College of Pharmacy, University of Illinois at Chicago (Research Methods in Pharmacognosy, Advanced Pharmacognosy I, II, III, Chemotaxonomy, Structure Elucidation of Natural Products I, II)
Continuing Education-	1980-1981	Lecture to Illinois pharmacists, various locations, "Insulin and Oral Sulfonylurea Therapy"

MAJOR RESEARCH INTERESTS:

1. Isolation, identification, structure elucidation and bioassay of biologically active plant constituents, in particular those with a sweet taste, and those with anticancer, antiviral, and skin-irritant activity.

2. Chemotaxonomy (comparative phytochemistry) of plant alkaloids and terpenoids.

3. Phytochemical and toxicological studies on poisonous plants.

4. Qualitative and quantitative methods of analysis of plant constituents.

FIELD EXPERIENCE:

Visit to northern and central Nigeria to collect latex of succulent Euphorbia species for research, September, 1974.

Visit to Paraguay, Argentina, and Costa Rica to collect plants with a sweet taste, August, 1987.

SERVICE ON NATIONAL COMMITTEES OF SCIENTIFIC SOCIETIES

American Chemical Society, Agricultural and Food Chemistry Division -
Secretary, Agricultural and Natural Products Chemistry Subdivision, 1992

American Society of Pharmacognosy -
Constitution and By-Laws Committee, Member, 1981-1983
Executive Committee, Member, 1985-1988, 1991-1992
Nominating Committee, Chairman, 1991-1992
Organizing Committee, 32nd Annual Meeting, Member, 1991
Patrons Committee, Chairman, 1990-1991
Past-President, 1991-1992
President, 1990-1991
Scientific Program Committee, Chairman, 32nd Annual Meeting, 1991

Vice President, 1989-1990

American Society of Pharmacognosy Foundation Board - Vice-Chairman, 1990-1992
Chairman, 1991-1992

Society for Economic Botany -
- Ad hoc Awards Committee, Member, 1987-1988, 1990-1991; Chairman, 1989-1990
- Ad hoc Future Directions Committee, Chairman, 1991-1992
- Education and Outreach Committe, Chairman, 1991-1992
- Member of Council, 1983-1984
- Nominating Committee, Member, 1979-1980, 1987-1988
- President-elect, 1990-1991
- President, 1991-1992
- Program Committee, Member, 1976-1977, 1979-1980; Chairman, 1984-1987
- Program and Publiity Committee, Chairman, 1991-1992
- Publicity Committee, 1990-1991
- Secretary, 1984-1987
- Scientific Program Committee, Chairman, 33rd Annual Meeting, 1992
- Vice President, 1989-1990

SERVICE ON CAMPUS COMMITTEES, UNIVERSITY OF ILLINOIS AT CHICAGO

- Ad hoc Committee on Campus Research Resources and Facilities, Subcommittee on Mass Spectrometry, 1982
- Ad hoc Committee to Review Graduate Program in Oral Pathology, 1988
- Ad hoc Credentials Committee, Specialized Center for Cancer Research, Chairman, 1991-1992
- Advisory Committee, Mass Spectrometry Laboratory, 1983-1986
- Advisory Committee, Research Resources Center, 1986-1988; 1990-1993
- Campus Research Board, Basic Life Sciences Subcommittee (Intramural Grant Reviews), 1986-1992
- Clinical Promotion and Tenure Committee, 1988-1989
- Executive Committee, Graduate College, 1987-1988
- Life Sciences Graduate Divisional Committee, 1987-1988
- Pew Scholar Selection Committee, 1987

SERVICE ON COMMITTEES, COLLEGE OF PHARMACY, UNIVERSITY OF ILLINOIS AT CHICAGO

College -
- Academic Standing Committee, 1978-1980
- ACPE Accreditation Self-Study Committee, Sub-Committee C (Curriculum, Students, and Evaluation), 1980-1981
- Ad hoc Research and Graduate Education Committee, 1982, 1984
- Ad hoc Self-Study Committee for ACPE Accreditation, 1986-1988
- Ad hoc Webster-Sibilsky Lectureship Committee, 1982, 1984
- Continuing Education Committee, 1978-1979

Committee on Committees, 1988-1989
Committee to Select Replacement NMR Instrument, 1983-1984
Executive Committee, 1983-1985
Graduate Education Steering Committee, 1985-1986
Graduate Education Steering Committee, Subcommittee on the Proposed Pharm.D./Ph.D. Curriculum (Chairman), 1985-1986
Scholarships and Awards Committee, 1980-1984
Task Force on Departmental Reorganization, 1982
Task Force on Graduate Education, 1983-1985

Departmental - Advisory Committee, Department of Pharmacognosy and Pharmacology, 1981-1982
Advisory Committee, Department of Medicinal Chemistry and Pharmacognosy, 1982-1985, 1986-1992
Advisory Committee on Promotions and Tenure (Chairman), 1984

Ad hoc Committee on Curriculum for Graduate Program in Pharmacognosy (Chairman), 1988
Ad hoc Curriculum Committee, Department of Medicinal Chemistry and Pharmacognosy, 1981-1982
Graduate Committee, Department of Pharmacognosy and Pharmacology, 1981-1982
Graduate Education Committee, Program in Pharmacognosy, 1984-1988
Research and Graduate Committee, Program in Pharmacognosy, 1977-1984
Search Committees, Assistant Professor of Medicinal Chemistry, 1984-1985; 1986; 1989-1990
Search Committee, Assistant Professor of Pharmacognosy (Chairman), 1984
Search Committee for Head, Department of Medicinal Chemistry and Pharmacognosy, 1987-1988

SCIENTIFIC SYMPOSIUM ORGANIZATION

Organizer of symposia for the Society for Economic Botany on "Toxic Plants" (1977, University of Miami, Coral Gables) and "Legumes" (1980, Indiana University, Bloomington, Indiana).
Symposium Chairman, Norman R. Farnsworth Symposium on Natural Products Research (March 24, 1990, Chicago, Illinois).
Organizer of symposium entitled "Human Medicinal Agents from Plants", 203rd Annual meeting, American Chemical Society, Division of Agricultural and Food Chemistry, San Francisco, California, April 6-10, 1992.

JOURNAL RESPONSIBILITIES

North American Regional Editor (Co-Editor) and Member of the Editorial Advisory Board of Phytochemical Analysis. (An international journal of plant chemical and biochemical techniques, John Wiley & Sons, Chichester, U.K.) (1989-).
Member of the Editorial Advisory Board of Journal of Research & Education in Indian Medicine (Varanisi, India) (1990-).
Member of the Editorial Advisory Board of Journal of Natural Toxins (Alaken Inc., Ft. Collins, Colorado) (1990-).
Member of the Editorial Advisory Board of Phytotherapy Research (John Wiley & Sons, Chichester, U.K.) (1990-).

Referee for submitted papers to Biochemical Systematics and Ecology, Botanical Gazette, Chemical Reviews, CRC Critical Reviews in Food Science, Economic Botany, International Journal of Pharmacognosy, Journal of Agricultural and Food Chemistry, Journal of Chemical Education, Journal of Ethnopharmacology, Journal of Natural Products, Journal of Pharmaceutical Sciences, Pharmaceutical Research, Phytochemical Analysis, Phytochemistry, Planta Medica, South African Journal of Botany.

CONSULTANCIES, GRANT REVIEWING, AND EXTERNAL EXAMINING

Consultant, A.J. Canfield Co., Chicago, Illinois, 1980

Consultant, American Ginseng Company, Chicago, Illinois, 1981

Consultant, ABIC International Consultants, Inc., Pine Brook, New Jersey, 1982

Consultant, Kirkland and Ellis, Attorneys-at-Law, Washington, D.C., 1982

Grant Reviewer, Campus Research Board, University of Illinois at Chicago, 1983, 1984, 1986, 1987, 1990, 1991

Consultant, Computer Sciences Corporation, NSTL Station, Mississippi, 1984

Grant Reviewer, Research Corporation, New York, New York, May, 1984

Grant Reviewer, National Science Foundation, Division of International Programs, April, 1984, October, 1985

External Examiner, Ph.D. Thesis of N. Indrani ("Studies on Vegetable Tannins and Proteins"), Faculty of Botany, University of Madras, Madras, India, 1984

Consultant, Douglas Bristol, Attorney-at-Law, Chicago, Illinois, 1985

External Examiner, Ph.D. Thesis of M.I. Tyler ("Antitumor and Piscicidal Esters of Naturally Occurring Daphnanes"), Faculty of Chemistry, Macquarie University, North Ryde, New South Wales, Australia, 1985

Consultant, General Foods Corporation, White Plains, New York, 1986

Consultant, NBC Defense and Technology International, New York, New York, 1986

Grant Reviewer, American Society of Pharmacognosy, 1986

Consultant, Sverdrup Technology, Inc., NSTL Station, Mississippi, 1987

Grant Reviewer, National Science Foundation, Program for Synthetic Organic Chemistry, May, 1988

Member, National Institutes of Health, Experimental Therapeutics-2 (AHR-B1) Study Section, July, 1988

Member, National Institutes of Health, Medicinal Chemistry (AHR-B1) Study Section, December, 1988

Ad hoc Member, National Institutes of Health, Bio-organic and Natural Product Chemistry Study Section, February, 1989

External Examiner, Ph.D. Thesis of K. Vasisht, ("Quassinoids and Alkaloids of Certain Ailanthus Species of Indian Origin"), Faculty of Pharmaceutical Sciences, Panjab University, Chandigarh, India, 1989

Consultant, Weil, Gotshal & Manges, Attorneys-at-Law, Washington, D.C., 1989

Member, National Institutes of Health, Experimental Therapeutics-2 (AHR-B1) Study Section, August, 1989

Grant Reviewer, Petroleum Research Fund, American Chemical Society, October, 1989

Member, National Institutes of Health, Experimental Therapeutics-2 (AHR-B1) Study Section, March, 1990

Member, National Institutes of Health, Medicinal Chemistry (AHR-B1) Study Section, November, 1990

Member, Special Review Committee, Biological and Chemical Studies on Taxol, National Cancer Institute, National Institutes of Health, March, 1991

Member, Special Review Committee, National Institutes of Health Research Centers in Minority Institutions, University of Puerto Rico, Rio Piedras, Puerto Rico, May, 1991

Grant Reviewer, Division of Extramural Activities, National Cancer Institute, National Institutes of Health, July, 1991

Ad hoc Member, National Institutes of Health AIDS and Related Diseases-D Study Section, San Diego, California, Noember, 1991

Consultant, Proctor and Gamble, Inc., Miami Valley Laboratories, Cincinnati, Ohio, 1991

FORMER GRADUATE STUDENTS

Dr. Ahmed A. Seida (Co-Thesis Advisor), Ph.D., University of Illinois at the Medical Center (1978).
Dissertation Title: "Isolation, Identification and Structure Elucidation of Cytotoxic and Antitumor Principles from Ailanthus integrifolia, Amyris pinnata and Balanites aegyptiaca"
Present Position: Associate Professor, College of Pharmacy, Cairo University, Cairo, Egypt

Dr. Ibrahim I. Mahmoud (Thesis Advisor), Ph.D., University of Illinois at the Medical Center (1979)
Dissertation Title: "Phytochemical Studies of Capisicodendron dinissi (Canellaceae) and Cerbera manghas (Apocynaceae)"
Present Position: Associate Professor, College of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan

Dr. Thomas A. Hickey (Major and Thesis Advisor), M.S., University of Illinois at the Medical Center (1981)
Thesis Title: "A Phytochemical and Toxicological Investigation of Euphorbia

hermentiana Lem.
Present Position: Physician

Dr. Manuel F. Balandrin (Major and Thesis Advisor), Ph.D., University of Illinois at the Medical Center (1982)
Dissertation Title: "Structure Elucidation of Some Biologically Active Constituents of the Genus Acosmium (Leguminosae)
Present Position: Senior Natural Products Chemist, Natural Products Sciences, Salt Lake City, UT

Ms. Helena C. Makapugay (Major and Thesis Advisor), M.S., University of Illinois at Chicago (1983)
Thesis Title: "High Pressure Liquid Chromatography of the Sweet Principles of Stevia rebaudiana and Thladiantha grosvenori"
Present Position: Pharmaceutical Engineer, Syntex, Palo Alto, CA

Dr. Gary T. Marshall (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago (1985)
Dissertation Title: "New Phorbol Constituents from Croton Oil"
Present Position: Applications Chemist, Interaction Chemicals, Mountain View, CA

Dr. Cesar M. Compadre (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago (1985)
Dissertation Title: "Studies on the Sweet Principle of Lippia dulcis and on Steviol, the Aglycone of Stevioside"
Present Position: Assistant Professor, College of Pharmacy, University of Arkansas for Medical Sciences, Little Rock, AR

Dr. Lee-Juian Lin (Co-Thesis Advisor), Ph.D., University of Illinois at Chicago (1986)
Dissertation Title: "Studies in Natural Product Structure Elucidation and Synthesis"
Present Position: Research Associate, College of Pharmacy, University of Illinois at Chicago, IL

Dr. Chang-Yih Duh (Major Advisor, Co-Thesis Advisor), Ph.D., University of Illinois at Chicago (1986)
Dissertation Title: "Phytochemical and Mechanistic Studies on Constitutents of Wikstroemia elliptica and Stizophyllum riparium"
Present Position: Associate Professor, School of Pharmacy, Kaohsiung Medical College, Kaohsiung, Taiwan

Dr. Young-Hee Choi (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago (1988)
Dissertation Title: "Biologically Active Constituents of Agrostistachys hookeri and Abrus precatorius"
Present Position: Lecturer in Pharmacognosy, College of Pharmacy, Ehwa Women's University, Seoul, Korea

Dr. Jinwoong Kim (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago (1988)
Dissertation Title: "Structure Elucidation of Sweet and Bitter Principles of Polypodium glycyrrhiza"
Present Position: Assistant Professor, College of Pharmacy, Seoul National University, Seoul, Korea

Dr. Mamdouh M. Ahmed (Co-Supervisor), Ph.D., Mansoura University, Egypt (1990)
Dissertation Title: "A Phytochemical Study of Certain Plants Belonging to the Genus Verbascum Growing in Egypt"
Present Position: Lecturer in Pharmacognosy, Mansoura University, Mansoura, Egypt

Dr. Charles M. Nshimo (Thesis Advisor), Ph.D., University of Illinois at Chicago (1991)
Dissertation Title: "Phytochemical and Biological Studies on Muntingia calabura"
Present Position: Lecturer, Division of Pharmaceutical Sciences, University of Dar-es-Salaam, Dar-es-Salaam, Tanzania

Dr. Leonardus B.S. Kardono (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago, 1992
Dissertation Title: "Structure Elucidation of Bioactive Constituents of Two Indonesian Medicinal Plants"
Present Position: Staff Scientist, Research and Dvelopment Center for Applied Chemistry, Indonesian Research and Development Center, Tangerang, Indonesia

Dr. Fekadu Fullas (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago, 1992
Dissertation Title: "Structure Elucidation of Bioactive Constituents of Baccharis gaudichaudiana
Present Position: Postdoctoral Research Associate, Research Triangle Institute, Research Triangle Park, North Carolina

Dr. Jin-Rui Dai (Major and Thesis Advisor), Ph.D., University of Illinois at Chicago, 1992
Dissertation Title: "Cytotoxic Consituents of Three South American and Indonesian Medicinal Plants"
Present Position: Postdoctoral Research Scientist, Xechem, Inc., New Brunswick, New Jersey

FORMER POSTDOCTORALS/VISITING SCHOLARS

Dr. M.A. Selim, University of Cairo, Cairo, Egypt, 1978.

Dr. M. Arisawa, Toyama Medical and Pharmaceutical University, Toyama, Japan, 1981-1982.

Professor S.S. Handa, Panjab University, Chandigarh, India, 1981-1982.

Dr. N.P.D. Nanayakkara, University of Peradeniya, Sri Lanka, 1981-1987.

Associate Dean Guo Ji-Xian, Shanghai First Medical College, Shanghai, People's Republic of China

Associate Dean Yang Peiquan, Sichuan Medical College, Chengdu, People's Republic of China, 1983-1984.

Dr. C.-T. Che, University of Illinois at Chicago, 1983-1985.

Dr. M. Fiebig, University of Munich, W. Germany, 1984-1985.

Dr. R.A. Hussain, University of Strathclyde, Glasgow, Scotland, 1985-1988.

Mr. M.E. Hossain, BCSIR Laboratories, Bangladesh, 1985.

Dr. C.A.J. Erdelmeier, ETH, Zurich, Switzerland, 1985-1986.

Professor Dr. D.W. Bishay, Assiut University, Assiut, Egypt, 1985-1986.

Dr. S.L. Leung, National University of Singapore, Singapore, 1986.

Lui Shengquan, Heilongjiang Academy of Chinese Traditional Medicine, Harbin, People's Republic of China, 1986-1987.

Dr. Y.-M. Lin, Academica Sinica, Taipei, Taiwan, 1987-1988.

Dr. M.M. Ahmed, Mansoura University, Mansoura, Egypt, 1987-1989.

Dr. P. Rasoanaivo, University of Antananarivo, Madagascar, 1989-1990.

Dr. N. Kaneda, Hiroshima University, Hiroshima, Japan, 1989-1991.

Dr. A. Pervin, University of Karachi, Karachi, Pakistan, 1991.

PRESENT POSTDOCTORALS/VISITING SCHOLARS

Mrs. X.-J. Ma, 4th Pharmaceutical Works, Shanghai, People's Republic of China, 1990-present.

Dr. D.B.M. Wickramaratne, University of Peradeniya, Peradeniya, Sri Lanka, 1991-present.

Dr. Myung Sook Chung, Seoul National University, Seoul, Korea, 1991-present.

Dr. Kio A. Abo, University of Ibadan, Ibadan, Nigeria, 1991-present.

Dr. Ik-Soo Lee, University of Mississippi, University, MS, 1991-present.

Dr. L. Luyengi, Free University of Brussels, Brussels, Belgium, 1991-present.

PRESENT GRADUATE STUDENTS

Mr. M.P. Nasution, Major Advisor, 1986-present. (Expected graduation date, 1992).

Miss Tan Ghee Teng, Major Advisor, 1988-present. (Expected graduation date, 1992).

Mr. R. Suttistri, Major and Thesis Advisor, 1989-present. (Expected graduation date, 1993).

Mr. Z.H. Mbwambo, Major and Thesis Advisor, 1991-present. (Expected graduation date, 1995).

PUBLICATIONS

A. Research Articles

1. Evans, F.J. and A.D. Kinghorn. 1973. Thin-layer chromatographic behavior of the acetates of some polyfunctional diterpene alcohols of toxicological interest. J. Chromatogr. 87:443-448.

2. Evans, F.J. and A.D. Kinghorn. 1974. Ingenol from Euphorbia desmondii. Phytochemistry 13:1011.

3. Kinghorn, A.D. and F.J. Evans. 1974. A quantitative gas-liquid chromatographic method for phorbol and related diterpenes as their acetates. J. Pharm. Pharmac. 26:408-412.

4. Evans, F.J. and A.D. Kinghorn. 1974. A new ingenol type diterpene from the irritant fractions of Euphorbia myrsinites and Euphorbia biglandulosa. Phytochemistry 13:2324-2325.

5. Kinghorn, A.D. and F.J. Evans. 1974. Occurrence of ingenol in Elaeophorbia species. Planta Med. 26:150-154.

6. Kinghorn, A.D. and F.J. Evans. 1975. Isolation of phorbol from Euphorbia frankiana. Phytochemistry 14:585-586.

7. Kinghorn, A.D. and F.J. Evans. 1975. Skin irritants of Euphorbia fortissima. J. Pharm. Pharmac. 27:329-333.

8. Evans, F.J. and A.D. Kinghorn. 1975. New diesters of 12-deoxyphorbol. Phytochemistry 14:1669-1670.

9. Evans, F.J., A.D. Kinghorn, and R.J. Schmidt. 1975. Some naturally occurring skin irritants. Acta Pharmacol. et Toxicol. 37:250-256.

10. Evans, F.J., R.J. Schmidt and A.D. Kinghorn. 1975. A micro-technique for the identification of diterpene ester inflammatory toxins. Biomed. Mass Spectrom. 2:126-130.

11. Evans, F.J. and A.D. Kinghorn. 1975. The succulent Euphorbias of Nigeria. Part I. Lloydia 38:363-365.

12. Kinghorn, A.D. and F.J. Evans. 1975. A biological screen of selected species of the genus Euphorbia for skin irritant effects. Planta Med. 28:325-335.

13. Evans, F.J. and A.D. Kinghorn. 1977. A comparative phytochemical study of the diterpenes of some species of the genera Euphorbia and Elaeophorbia (Euphorbiaceae). J. Linn. Soc. London Bot. 74:23-35.

14. Kinghorn, A.D., K.K. Harjes and N.J. Doorenbos. 1977. Screening procedure for phorbol esters using brine shrimp (Artemia salina) larvae. J. Pharm. Sci. 66:1362-1363.

15. Jawad, F.H., A.D. Kinghorn, N.J. Doorenbos and S. Billets. 1977. Characterization and mass spectral analysis of some grayanotoxin derivatives. Biomed. Mass Spectrom. 4:331-336.

16. Ogura, M., G.A. Cordell, A.D. Kinghorn and N.R. Farnsworth. 1977. Potential anticancer agents VI. Constituents of Ailanthus excelsa (Simaroubaceae). Lloydia 40:579-584.

17. Kinghorn, A.D., F.H. Jawad and N.J. Doorenbos. 1978. Thin-layer chromatographic and spectroscopic characterization of some diterpenes of the grayanotoxin type. J. Chromatogr. 147:299-308.

18. Kinghorn, A.D., F.H. Jawad and N.J. Doorenbos. 1978. Structure-activity relationship of grayanotoxin derivatives using a tetrodotoxin-antagonized spasmodic response of brine shrimp larvae (Artemia salina). Toxicon 16:227-234.

19. Balandrin, M.F., A.D. Kinghorn, S.J. Smolenski and R.H. Dobberstein. 1978. Reversed-phase high-pressure liquid chromatography of some tryptamine derivatives. J. Chromatogr. 157:365-370.

20. Seida, A.A., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1978. Potential anticancer agents IX. Isolation of a new simaroubolide, 6α-tigloyloxychaparrinone, from Ailanthus integrifolia ssp. calycina, Lloydia 41:584-587.

21. Kinghorn, A.D. 1979. Characterization of an irritant 4-deoxyphorbol diester from Euphorbia tirucalli. J. Nat. Prod. 42:112-115.

22. Svoboda, K.S., S.J. Smolenski and A.D. Kinghorn. 1979. Indole alkylamines from Tachigalia paniculata. J. Nat. Prod. 42:307-308.

23. Kinghorn, A.D. and S.J. Smolenski. 1980. Alkaloids of Lupinus bicolor ssp. microphyllus. Detection of 5,6-dehydro-α-isolupanine by gas chromatography-mass spectrometry. Planta Med. 38:280-282.

24. Mahmoud, I.I., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1980. Potential anticancer agents. XVI. Isolation of bicyclofarnesane sesquiterpenoids from Capsicodendron dinisii. J. Nat. Prod. 43:365-371.

25. Kinghorn, A.D., M.A. Selim and S.J. Smolenski. 1980. Alkaloid distribution in some New World Lupinus species. Phytochemistry 19:1705-1710.

26. Kinghorn, A.D. 1980. Major skin-irritant principle from Synadenium grantii. J. Pharm. Sci. 69:1446-1447.

27. Worobec, S.M., T.A. Hickey, A.D. Kinghorn, D.D. Soejarto and D.P. West. 1981. Irritant contact dermatitis from an ornamental Euphorbia. Contact Dermatitis 7:19-22.

28. Marshall, G.T. and A.D. Kinghorn. 1981. Isolation of phorbol and 4α-phorbol from croton oil by droplet counter-current chromatography. J. Chromatogr., 206:421-424.

29. Balandrin, M.F. and A.D. Kinghorn. 1981. Tetrahydrorhombifoline, a further constituent of Lupinus oscar-haughtii and L. truncatus. J. Nat. Prod. 44:495-497.

30. Badawi, M.M., A.A. Seida, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1981. Potential anticancer agents. XVIII. Constituents of Amyris pinnata. J. Nat. Prod. 44:331-334.

31. Seida, A.A., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1981. Isolation of bergapten and marmesin from Balanites aegyptiaca. Planta Med. 43:92-93.

32. Gunasekera, S.P., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1981. Potential anticancer agents. XIX. Constituents of Aquilaria malaccensis. J. Nat. Prod. 44:569-572.

33. Balandrin, M.F. and A.D. Kinghorn. 1981. Characterization of sweetinine, a constituent of Sweetia elegans, as the Ormosia alkaloid, (±)-6-epipodopetaline. J. Nat. Prod. 44:619-622.

34. Hickey, T.A., S.M. Worobec, D.P. West and A.D. Kinghorn. 1981. Irritant contact dermatitis in humans from phorbol and related esters. Toxicon 19:841-850.

35. Huang, Z-J., A.D. Kinghorn and N.R. Farnsworth. 1982. Studies on herbal remedies I. Analysis of herbal smoking preparations alleged to contain lettuce (Lactuca sativa L.) and other natural products. J. Pharm. Sci., 71:270-271.

36. Kinghorn, A.D., N.P.D. Nanayakkara, D.D. Soejarto, P.J. Medon and S.K. Kamath. 1982. Potential sweetening agents of plant origin. I. Purification of Stevia rebaudiana sweet constituents by droplet counter-current chromatography. J. Chromatogr. 237:478-483.

37. Kinghorn, A.D., M.F. Balandrin and L.-J. Lin. 1982. Alkaloid distribution in some species of the papilionaceous tribes Sophoreae, Dalbergieae, Loteae, Brongniartieae and Bossiaeeae. Phytochemistry, 21:2269-2275.

38. Kim, I-C., M.F. Balandrin and A.D. Kinghorn. 1982. Reinvestigation of alkaloids of Lupinus sericeus Pursh. Identification of a new natural product, 10,17-dioxo-β-isosparteine. J. Agric. Food Chem., 30:796-798.

39. Soejarto, D.D., A.D. Kinghorn and N.R. Farnsworth. 1982. Potential sweetening agents of plant origin. III. Organoleptic evaluation of Stevia leaf herbarium samples for sweetness. J. Nat. Prod. 45:590-599.

40. Balandrin, M.F. and A.D. Kinghorn. 1982. (-)-4α-Hydroxysparteine, a new natural product from Acosmium panamense. Heterocycles, 19:1931-1934.

41. Balandrin, M.F., E.F. Robbins and A.D. Kinghorn. 1982. Alkaloid distribution in some species of the papilionaceous tribes Thermopsideae and Genisteae. Biochem. Syst. Ecol., 11:307-311.

42. Soejarto, D.D., C.M. Compadre, P.J. Medon, S.K. Kamath and A.D. Kinghorn. 1983. Potential sweetening agents of plant origin. II. Field search for sweet-tasting Stevia species. Econ. Bot., 37:71-79.

43. Makapugay, H.C., D.D. Soejarto, A.D. Kinghorn and E. Bordas. 1983. Piperovatine, the tongue-numbing principle of Ottonia frutescens. J. Ethnopharmacol., 7:235-238.

44. Handa, S.S., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1983. Plant anticancer agents. XXII. Isolation of a phorbol diester and its $\Delta^{5,6}$-7β-hydroperoxide derivative from Ostodes paniculata. J. Nat.Prod., 46:123-126.

45. Lin, L.-J. and A.D. Kinghorn. 1983. Three new ingenane esters from the latex of Euphorbia canariensis L. J. Agric. Food Chem., 31:396-400.

46. Arisawa, M., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1983. Plant anticancer agents XXIII. 6α-Senecioyloxychapparin, a new antileukemic quassinoid from Simaba multiflora. J. Nat. Prod., 46:218-221.

47. Arisawa, M., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1983. Plant anticancer agents XXIV. Alkaloid constituents of Simaba multiflora. J. Nat. Prod., 46:222-225.

48. Handa, S.S., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1983. Plant anticancer agents XXV. Constituents of Soulamea soulameoides. J. Nat. Prod., 46:359-364.

49. Handa, S.S., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1983. Plant anticancer agents XXVI. Constituents of Peddiea fischeri. J. Nat. Prod., 46:248-250.

50. Badawi, M.M., S.S. Handa, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1983. Plant anticancer agents XXVII. Antileukemic and cytotoxic constituents of Dirca occidentalis (Thymelaeaceae). J. Pharm. Sci., 72:1285-1287.

51. Bhacca, N.S., M.F. Balandrin, A.D. Kinghorn, T.A. Frenkiel, R. Freeman and G.A. Morris. 1983. Carbon-13 and proton two-dimensional NMR study of the Ormosia alkaloids panamine, ormosanine and ormosinine. J. Amer. Chem. Soc., 105:2538-2544.

52. Lin, L.-J., G.T. Marshall and A.D. Kinghorn. 1983. The dermatitis-producing constituents of Euphorbia hermentiana latex. J. Nat. Prod., 46:723-731.

53. Lin, L.-J. and A.D. Kinghorn. 1983. 8-Methoxyingol esters from the latex of Euphorbia hermentiana. Phytochemistry, 22:2795-2799.

54. Makapugay, H.C., N.P.D. Nanayakkara and A.D. Kinghorn. 1984. Improved high-pressure liquid chromatographic separation of the Stevia rebaudiana sweet diterpene glycosides using linear gradient elution. J. Chromatogr., 283:390-395.

55. Arisawa, M., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1984. Ipomopsin, a new biscoumarin from Ipomopsis aggregata. J. Nat. Prod., 47:106-112.

56. Arisawa, M., J.M. Pezzuto, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1984. Plant anticancer agents XXX. Cucurbitacins from Ipomopsis aggregata (Polemoniaceae). J. Pharm. Sci., 73:411-413.

57. Arisawa, M., S. Funiyama, J.M. Pezzuto, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. 1984. Plant anticancer agents XXXII. Hydroquinone from Ipomopsis aggregata. J. Nat. Prod., 47:393-394.

58. Kinghorn, A.D., D.D. Soejarto, N.P.D. Nanayakkara, C.M. Compadre, H.C. Makapugay, J.M. Hovanec-Brown, P.J. Medon and S.K. Kamath. 1984. A phytochemical screening procedure for sweet ent-kaurene glycosides in the genus Stevia. J. Nat. Prod., 47:439-444.

59. Guo, J.-X., S.S. Handa, J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. 1984. Plant anticancer agents XXXIII. Constituents of Passerina vulgaris. Planta Med., 50:264-265.

60. Marshall, G.T. and A.D. Kinghorn. 1984. Short-chain phorbol ester constituents of croton oil. J. Am. Oil. Chem. Soc., 61:1220-1225.

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b. Review Articles

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E. Patents

1. Kinghorn, A.D. and G.T. Marshall. Purification of 12-O-tetradecanoyl-phorbol-13-acetate, phorbol and 4α-phorbol from croton oil. U.S. Patent 4,468,328, August 28, 1984.

2. Kinghorn, A.D., C.M. Compadre and J.M. Pezzuto. Low cariogenic sweetening agents. U.S. Patent 4,808,409, February 28, 1989.

3. Kinghorn A.D. and Y.-H. Choi. Novel intense natural sweeteners. Japanese patent application No. 2652/1990, filed January 11, 1990.

4. Kinghorn, A.D. and Y.-H. Choi. Novel intense natural sweeteners. U.S. patent application No. 549,776, filed July 9, 1990.

5. Kinghorn, A.D. and Y.-H. Choi. Novel intense natural sweeteners. Canadian patent application No. 2,020,772, filed July 9, 1990.

F. Book Reviews

1. "Aromatic Plants: Basic and Applied Aspects", eds. N. Margaris, A. Koedam and D. Vokou, Martinus Nijhoff, The Hague, Netherlands, 1982, pp. 284. (J. Nat. Prod. 46:600, 1983).

2. "The Chemistry and Biology of Isoquinoline Alkaloids", eds. J.D. Phillipson, M.F. Roberts and M.H. Zenk, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo, 1985, pp. 304. (Quart. Rev. Biol., 61:256-257, 1986).

3. "Peptides of Poisonous Amanita Mushrooms", by T. Wieland, Springer-Verlag, New York, 1986, pp. 256. (Quart. Rev. Biol., 62:308-309, 1987).

4. "Medicinal Plants in Tropical West Africa", by B. Oliver-Bever, Cambridge University Press, New York, 1985, pp. 375. (J. Nat. Prod., 51:627, 1988).

5. "Naturally Occurring Phorbol Esters", ed. F.J. Evans, CRC Press, Boca Raton, Florida, 1986, pp. 313. (J. Nat. Prod., 52:221, 1989).

6. "The Alkaloids: Chemistry and Pharmacology", vol. 32, ed. A. Brossi, Academic Press, San Diego, California, 1988, pp. 454. (Quart. Rev. Biol., 64:374-375, 1989).

7. "Biologically Active Natural Products: Potential Use in Agriculture". ACS Symposium Series 380, ed. H.C. Cutler, American Chemical Society, Washington, D.C., 1988, pp. 483. (Econ. Bot., 44:285, 1990).

8. "Principles and Practice of Chromatography", by B. Ravindranath, Halsted Press, John Wiley & Sons, New York, 1989, pp. 502. (J. Nat. Prod., 53:224, 1990).

9. "Drug Discovery: the Evolution of Modern Medicines", by W. Sneader, John Wiley and Sons, Chichester, U.K., 1985, pp. 485. (Int. J. Crude Drug Res., 28, 272, 1990).

10. "Plant Polyphenols: Vegetable Tannins Revisited", by E. Haslam, Cambridge University Press, New York, 1989, pp. 230. (Econ. Bot., 45:140-141, 1991).

11. "With Bitter Herbs They Shall Eat It: Chemical Ecology in the Origins of Human Diet and Medicine", by T. Johns, University of Arizona Press, Tucson, Arizona, 1990, pp. 356 (Econ. Bot., 45, in press).

12. "Chromatographic Analysis of Alkaloids", Chromatographic Science Series No. 53, by M. Popl, J. Fähnrich, and V. Tatar, Marcel Dekker, New York, 1990, pp. 667 (J. Am. Chem. Soc., 113, 9014, 1991).

13. "Lignans: Chemical, Biological, and Clinical Properties", by D.C. Ayres and J.D. Loike, Cambridge University Press, New York, 1990, pp. 402 (Econ. Bot., 45, 441-442, 1991).

14. "Alkaloids: Chemical and Biological Perspectives", vol 7, ed. S.W. Pelletier, Springer-Verlag, New York, 1991, pp. 591. (Quart. Rev. Biol., 66, 496-497, 1991).

15. "Liquid Chromatography/Mass Spectrometry. Applications in Agricultural, Pharmaceutical and Environmental Chemistry", ed. M.A. Brown, ACS Symposium Series No. 420, American Chemical Society, Washington, D.C., 1990, pp. 298. (Phytochem. Anal., 2, 181, 1991).

16. "Carotenoids: Chemistry and Biology", eds. N.I. Krinsky, M. M. Mathews-Roth, and R.F. Taylor, Plenum, New York, 1989, pp. 382. (Pharm. Res., in press).

17. "Ecological Chemistry and Biochemistry of Plant Terpenoids", Proceedings of the Phytochemical Society of Europe 31, eds. J.B. Harborne and F.A. Thomas-Barberan, Clarendon Press, Oxford, U.K., 1991, pp. 439. (J. Nat. Prod., in press).

18. "Brassinosteroids. Chemistry, Bioactivity, & Applications", eds. H.G. Cutler, T. Yokota, and G. Adam, ACS Symposium Series No. 474, American Chemical Society, Washington, D.C., 1991, pp. 358. (Phytochem. Anal., in press).

G. Dissertation

1. Kinghorn, A.D. Some Biologically Active Constituents of the Genus Euphorbia. Ph.D. Dissertation, Faculty of Medicine, University of London. June, 1975, 237 pp.

H. Other

1. Soejarto, D.D., A.D. Kinghorn and N.R. Farnsworth. 1977. Letter to the Editor (Croton vs. Croton). Contact Dermatitis 3: 276.

2. Kinghorn, A.D. and C.M. Compadre. 1988. Hernandulcin: an Intensely Sweet Constituent of Lippia dulcis. The Herb Society of America News, Spring 1988, pp. 3-4.

3. Kinghorn, A.D. 1989. Letter to the Editor (Euphorbiaceous Wonder). Pharmaceutical Journal, February 11, pp. 154-155.

4. Kinghorn, A.D. and C.M. Compadre. 1990. Hernandulcin: el principio dulce de Lippia dulcis. Boletín ASAPLAM (San José, Costa Rica), No. 3, pp. 4-5. (In Spanish).

5. Pezzuto, J.M., A.D. Kinghorn, H.H.S. Fong, and G.A. Cordell (eds.). 1991. Progress on Terrestrial and Marine Natural Products of Medicinal and Biological Interest. Proceedings of a Symposium Held in Honor of the 60th Birthday of Professor Norman R. Farnsworth, American Botanical Council, Austin, Texas, 181 pp.

RESEARCH FUNDING:

1974
From: University of London Central Research Fund
Title: Travel Grant to Visit Nigeria to Collect Euphorbia Latex
Period: 09/04/74 - 09/30/74
Amount: $1500
Role: Co-Principal Investigator

1978
From: Campus Research Board, University of Illinois at the Medical Center
Title: Isolation of Biologically Active Diterpenes from the Plant Family Euphorbiaceae
Period: 09/01/78 - 06/30/79
Amount: $2906
Role: Principal Investigator

1979
From: National Cancer Institute, NIH
Title: Isolation of Antineoplastic Agents from Plants (CM-97295)
Period: 04/01/79 - 03/31/80
Amount: $142,275
Role: Senior Investigator

1980
From: National Cancer Institute, NIH
Title: Isolation of Antineoplastic Agents from Plants (CM-97295)
Period: 04/01/80 - 03/31/81
Amount: $140,241
Role: Senior Investigator

From: National Institute of Dental Research, NIH
Title: Studies to Identify, Isolate, Develop and Test Naturally Occurring Non-cariogenic Sweeteners that May be Used as Dietary Sucrose Substitutes (N01-DE-02425)
Period: 06/25/80 - 06/24/81
Amount: $76,316
Role: Principal Investigator

1981
From: National Cancer Institute, NIH
Title: Isolation of Antineoplastic Agents from Plants (CM-97295)
Period: 04/01/81 - 08/31/82
Amount: $154,564
Role: Senior Investigator (04/01/81 - 08/31/81)
Co-Principal Investigator (09/01/81 - 08/31/82)

From: National Institute of Dental Research, NIH
Title: Studies to Identify, Isolate, Develop and Test Naturally Occurring Non-cariogenic Sweeteners that May be Used as Dietary Sucrose Substitutes (N01-DE-02425)
Period: 06/25/81 - 06/24/82
Amount: $116,514
Role: Principal Investigator

1982
From: National Institute of Dental Research, NIH
Title: Studies to Identify, Isolate, Develop and Test Naturally Occurring Non-cariogenic Sweeteners that May be Used as Dietary Sucrose Substitutes (N01-DE-02425)

Period: 06/25/82 - 09/24/83
Amount: $125,378
Role: Principal Investigator

1983
From: National Cancer Institute, NIH
Title: Plant Antitumor Agents: Isolation and Identification (R01-CA-33047-01)
Period: 07/01/83-06/30/84
Amount: $98,665
Role: Co-Investigator (Acting Principal Investigator 12/01/83-05/31/84

1984
From: National Cancer Institute, NIH
Title: Plant Antitumor Agents: Isolation and Identification (R01-CA-33047-02)
Period: 07/01/84-06/30/85
Amount: $104,185
Role: Co-Investigator

From: Campus Research Board, Health Sciences Center, University of Illinois at Chicago
Title: Ultraviolet/Visible Spectrophotometer
Amount: $7,175
Role: Principal Investigator

1985
From: General Foods Corporation, White Plains, New York
Title: Isolation of Intensely Sweet Compounds from Plants (Year 1)
Period: 11/01/84-12/31/85
Amount: $67,630
Role: Principal Investigator

From: National Cancer Institute, NIH
Title: Plant Anticancer Agents: Isolation and Identification (R01-CA-33047-03)
Period: 07/01/85-06/30/86
Amount: $110,206
Role: Co-Investigator

1986
From: General Foods Corporation, White Plains, New York
Title: Isolation of Intensely Sweet Compounds from Plants (Year 2)
Period: 01/01/86-12/31/86
Amount: $67,630
Role: Principal Investigator

From: National Institute of Dental Research, NIH
Title: Evaluation of Natural Sweeteners Using the Mongolian Gerbil (R03-DE-07560-01)
Period: 02/01/86-07/31/87
Amount: $24,487
Role: Principal Investigator

1987
From: General Foods Corporation, White Plains, New York
Title: Isolation of Intensely Sweet Compounds from Plants (Year 3)
Period: 01/01/87-12/31/87
Amount: $90,415
Role: Principal Investigator

From: Campus Research Board, University of Illinois at Chicago
Title: Funds Towards the Purchase of an lto Separator-Extractor
Amount: $4,900
Role: Principal Investigator

From: Egyptian Cultural and Educational Bureau, Washington, D.C.
Title: Research Support for Mr. M.M. Ahmed (Mansoura University)
Period: 10/01/87-09/30/88
Amount: $4,000
Role: Preceptor

1988

From: General Foods Corporation, White Plains, New York
Title: Isolation of Intensely Sweet Compounds from Plants (Year 4)
Period: 01/01/88-06/30/88
Amount: $20,000
Role: Principal Investigator

From: Egyptian Cultural and Educational Bureau, Washington, D.C.
Title: Research Support for Mr. M.M. Ahmed (Mansoura University)
Period: 10/01/88-09/30/89
Amount: $4,000
Role: Preceptor

From: National Cancer Institute, NIH
Title: Plant Antitumor Agents: Isolation and Identification (R01-CA-33047-04)
Period: 12/01/88-11/30/89
Amount: $128,572
Role: Co-Investigator

1989

From: Wach Fund, College of Dentistry, University of Illinois at Chicago
Title: Effect of Two Sweeteners on Dental Caries
From: 07/01/89-06/30/90
Amount: $6,173
Role: Co-Investigator

From: National Cancer Institute, NIH
Title: Plant Antitumor Agents: Isolation and Identification (R01-CA-33047-05)
Period: 12/01/89-11/30/90
Amount: $134,272
Role: Co-Investigator

1990-

From: NcNeill Speciality Products Company, Skillman, New Jersey
Title: Unrestricted Gift for Research on Sweeteners
Amount: $5,000
Role: Principal Investigator

From: Abbott Laboratories, Abbott Park, Illinois
Title: Unrestricted Gift (Research Support for Mrs. X.-J. Ma)
Period: 03/01/90-02/28/91
Amount: $10,000
Role: Principal Investigator

From: Heyden & Son, London, U.K.
Title: Support for Editorial Duties for Phytochemical Analysis

Period: 07/01/01/89-12/31/90
Amount: $1,750
Role: North American Editor

From: National Cancer Institute, NIH
Title: Novel Strategies for Plant-Derived Anticancer Agents (U01-CA52956-01, National Cooperative Natural Product Drug Discovery Group Grant)
Period: 09/01/90-08/31/91
Amount: $87,980 (for Program 2, "Extraction, Fractionation, Isolation and Structure Elucidation", first year)
Role: Program Leader (Program 2)

From: National Cancer Institute, NIH
Title: Plant Antitumor Agents: Isolation and Identification (R01-CA-33047-06)
Period: 12/01/90-05/31/92
Amount: $134,772
Role: Co-Investigator

1991

From: John Wiley & Sons, Chichester, U.K.
Title: Support for Editorial Duties for Phytochemical Analysis
Period: 01/01/91-12/31/91
Amount: $1,000
Role: North American Editor

From: National Institute of Dental Research, NIH
Title: Noncariogenic Intense Natural Sweeteners (R01-DE-08937-01)
Period: 04/01/91-03/31/92
Amount: $126,481
Role: Principal Investigator

From: Kuraray International Corporation, New York
Title: Unrestricted Gift for Research on Sweeteners
Amount: $2,000
Role: Principal Investigator

From: Fogarty International Center, NIH
Title: Fellowship for Dr. K.A. Abo (F05-TW-04611-01)
Period: 08/01/91-07/31/92
Amount: $29,400
Role: Sponsor (Principal Investigator)

From: National Cancer Institute, NIH
Title: Small Instrumentation Grant (S15-CA55963-01)
Period: 08/01/91-07/31/92
Amount: $6,264
Role: Principal Investigator

From: National Cancer Institute, NIH
Title: Novel Stratgies for Plant-Derived Anticancer Agents (U01-CA-52956-02, National Cooperative Natural Product Drug Discovery Group Grant)
Period: 09/01/91-08/31/91
Amount: $150,612 (for Program 2, "Extraction, Fractionation, Isolation, and Structure Elucidation, second year)
Role: Program Leader (Program 2)

From:	National Cancer Institute, NIH
Title:	Natural Inhibitors of Carcinogenesis (Program Project, PO1 CA48112-01)
Period:	09/15/91-08/31/92
Amount:	$78,372 (for Program 2)
Role:	Program Leader (Program 2)

INVITED PRESENTATIONS

"Cocarcinogenic Irritant Euphorbiaceae." Symposium lecture at the 18th Annual Meeting of the Society for Economic Botany, Coral Gables, Florida, June, 1977.

"Alkaloids of Papilionoideae." Symposium lecture at the International Legume Conference, Kew Gardens, Richmond, U.K., July, 1978.

"Toxic Constituents of Legume Forage Plants." Symposium lecture at the 21st Annual Meeting of the Society of Economic Botany, Bloomington, Indiana, June, 1980. (Presented by S.J. Smolenski).

"Naturally Occurring Toxic Substances from Plants", Fall Semester Toxicology Seminar, Associated Colleges of the Chicago Area, Argonne National Laboratory, Argonne, Illinois, September 28, 1982.

"Studies on Some Plant-Derived Sweetening Agents", National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland, October 4, 1982.

"Stevia rebaudiana - the Sweet Herb of Paraguay", Plant Resources Institute, Salt Lake City, Utah, July 14, 1983.

"New Plant-Derived Anticancer Agents". Symposium lecture at the 43rd International Congress of Pharmaceutical Sciences of F.I.P., Montreux, Switzerland, September, 1983. (Pharmacy International, 4: 191, 1983).

"Potentials and Hazards of Plant-Derived Drugs", FIP Congress/Seminar for Scientific Journalists, Montreux, Switzerland, September 7, 1983.

"Medicinal Plants as Sources of Drugs and Pharmacologic Tools", Faculty of Health Sciences, Graduate Programme, McMaster University, Hamilton, Ontario, Canada, December 9, 1983.

"Skin-Irritant and Tumor-Promoting Compounds of Species of the Euphorbiaceae". Invited lecture at the Second Australia-United States Symposium on Poisonous Plants, Brisbane, Australia, May, 1984.

"Plant Toxins" (Two lectures), Toxin Symposium, U.S. Army Chemical Research and Development Command, Edgewood, Maryland, February, 1984.

"Intensely Sweet Terpenoids from Plants", Technical Center, General Foods Corporation, Tarrytown, New York, October 9, 1985.

"Hernandulcin: An Intensely Sweet Compound from Lippia dulcis", Calorie Control Council 18th Annual Meeting, Miami, Florida, October 22, 1985. (With C.M. Compadre and J.M. Pezzuto).

"Further Studies on Stevioside", Calorie Control Council 18th Annual Meeting, Miami, Florida, October 22, 1985. (With C.M. Compadre and J.M. Pezzuto).

"New Techniques for the Isolation, Identification and Biological Assessment of Plant Constituents", Department of Pharmacy, Institute of Technology, Bandung, Indonesia, November 2, 1985.

Dai, J.-R., J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn. "New Clerodane and Labdane Diterpenoids from Baccharis articulata". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by J.-R. Dai).

Dai, J.-R., L.B.S. Kardono, S. Tsauri, K. Padmawinata, J.M. Pezzuto, and A.D. Kinghorn. "Cytotoxic Phenylacetic Acid Derivatives from the Medicinal Plant Entada phaseoloides". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by J.-R. Dai).

Fullas, F., J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn. "New Cytotoxic Labdane and Clerodane Diterpene Constituents from Baccharis gaudichaudiana". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by F. Fullas).

Fullas, F., D.D. Soejarto, and A.D. Kinghorn. "Three Further Novel Diterpene Arabinosides from the Aerial Parts of Baccharis gaudichaudiana". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by F. Fullas).

Kaneda, N., H. Chai, J.M. Pezzuto, A.D. Kinghorn, N.R. Farnsworth, P. Tuchinda, J. Udchachon, T. Santisuk, and V. Reutrakul. "Cytotoxic Activity of Cardenolides from Beaumontia brevituba Oliver (Apocynaceae)". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by N. Kaneda).

Kardono, L.B.S., C.K. Angerhofer, S. Tsauri, K. Padmawinata, J.M. Pezzuto and A.D. Kinghorn. "Novel Cytotoxic and Antimalarial Alkaloids from the Roots of Eurycoma longifolia". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by L.B.S. Kardono).

Nasution, M.P. and A.D. Kinghorn. "Lupine Alkaloids from Ormosia krugii". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by M.P. Nasution).

Tan, G.T., A.D. Kinghorn, S.H. Hughes, and J.M. Pezzuto. "Psychotrine and Its Methyl Ether are Selective Inhibitors of Human Immunodeficiency Virus-1 Reverse Transcriptase". International Research Congress on Natural Products, Chicago, Illinois, July, 1991. (Presented by G.T. Tan).

Rodríguez, V., R. Pereda-Miranda, R. Mata, N. Kaneda, and A.D. Kinghorn. "New ent-Atisene Glycosides from the Roots of Stevia salicifolia Cav. (Asteraceae). 4th Chemical Congress of North America (202nd National Meeting of the American Chemical Society), New York, August, 1991. (Presented by V. Rodríguez).

Jakinovich, Jr., W., N.P.D. Nanayakkara, R.A. Hussain, and A.D. Kinghorn. "Stimulation of the Gerbil's Gustatory Receptors by Intense Natural Sweeteners". 19th Annual Meeting of the Society for Neuroscience, Phoenix, Arizona, October, 1989. (Presented by W. Jakinovich, Jr.; Society for Neuroscience Abstracts, 15: 753, 1989).

Hussain, R.A., F. Fullas, E. Bordas, J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn. "Structure-Sweetness Relationships of some Labdane-type Diterpene Glycosides from Baccharis gaudichaudiana". Bonn BACANS Meeting, Bonn, W. Germany, July, 1990. (Planta Med., 56: 497-498, 1990).

Tan, G.T., J.M. Pezzuto, and A.D. Kinghorn. "Evaluation of Natural Products as Potential Inhibitors of Human Immunodeficiency Virus (HIV) Reverse Transcriptase". Bonn BACANS Meeting, Bonn, W. Germany, July, 1990. (Presented by J.M. Pezzuto; American Pharmaceutical Association Kilmer Prize award lecture for G.T. Tan; Planta Med., 56: 504, 1990).

Nasution, M.P., R.A. Hussain, A.D. Kinghorn, A. Tosun, F. Tosun, M. Tanker, and T. Özden. "A New Type of Quinolizidine Alkaloid from Genista sessiliflora". Bonn BACANS Meeting, Bonn, W. Germany, July, 1990. (Planta Med., 56: 523, 1990).

Kardono, L.B.S., S. Tsauri, K. Padmawinata, J.M. Pezzuto, and A.D. Kinghorn. "Cytotoxic Constituents from Pacchyrhizus erosus". Bonn BACANS Meeting, Bonn, W. Germany, July, 1990. (Planta Med., 56: 673-674, 1990).

Pezzuto, J.M., C.W. Beattie, K. Lowell, W. Mar, S.M. Swanson, V. Reutrakul, A.D. Kinghorn, and N.R. Farnsworth. "Evaluation of the Cytotoxic Potential of Natural Products Employing a Battery of Human Cancer Cell Lines". Bonn BACANS Meeting, Bonn, W. Germany, July, 1990. (Presented by J.M. Pezzuto; Planta Med., 56: 673, 1990).

Kaneda, N., J.M. Pezzuto, D.D. Soejarto, A.D. Kinghorn, N.R. Farnsworth, P. Tuchinda, J. Udchachon, T. Santisuk, and V. Reutrakul. "New Cytotoxic Flavonoids from Muntingia calabura". Bonn BACANS Meeting, Bonn, W. Germany, July, 1990. (Presented by N. Kaneda; Planta Med., 56: 672-673, 1990).

Jakinovich, Jr., E. Vasquez, N.P. Nanayakkara, R.A. Hussain, and A.D. Kinghorn. "Taste Aversion to Intense Natural Sweeteners by the Gerbil". 20th Annual Meeting of the Society for Neuroscience, St. Louis, Missouri, October, 1990. (Presented by W. Jakinovich, Jr.; Society for Neuroscience Abstracts, 16: 879, 1990).

Das, S., A.K. Das, R.A. Murphy, A.D. Kinghorn, and I.C. Punwani. "Effect of Stevioside and Rebaudioside A on Dental Caries". 69th General Meeting of the International Association for Dental Research, Acapulco, Mexico, April, 1991. (Presented by S. Das; J. Dent. Res., 70: 576, 1991).

Schilling, A.D., V. Lanyon, R.A. Hussain, and A.D. Kinghorn. "Analysis of Some Derivatives of Steviol by Particle Beam LC/MS". 39th American Society of Mass Spectrometry Conference on Mass Spectrometry and Allied Topics, Nashville, Tennessee, May, 1991. (Presented by A.B. Schilling).

Novak, R.M., K.A. Keyer, A.D. Kinghorn, and J.M. Pezzuto. "Antiviral Activity of the Plant Compound Fagaronine Chloride, a Reverse Transcriptase Inhibitor in HIV-1 Infected Peripheral Blood Mononuclear Cells and T Cell Lines". VII International Conference on AIDS, Florence, Italy, June, 1991. (Presented by R.M. Novak).

Hussain, R.A., J. Kim, C.W.W. Beecher, and A.D. Kinghorn. "Unambiguous Assignment of the ^{13}C-NMR Spectra of Some Protoberberine Alkaloids and Their Tetrahydro Derivatives". International Congress on Natural Products Research, Park City, Utah, July, 1988. (Presented by R.A. Hussain).

Fullas, F., J. Kim, C.M. Compadre, N.P.D. Nanayakkara, R.A. Hussain, and A.D. Kinghorn. "Analytical and Preparative Separations of Some Natural Product Intense Sweeteners Using Overpressure Layer Chromatography". International Congress on Natural Products Research, Park City, Utah, July, 1988. (Presented by F. Fullas).

Hussain, R.A., L.M. Poveda A., J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn. "Phenylpropanoid Constituents of Some Sweet Plants". International Congress on Natural Products Research, Park City, Utah, July, 1988.

Kardono, L.B.S., S. Tsauri, K. Padmawinata, J.M. Pezzuto, and A.D. Kinghorn. "Cytotoxic Constituents of the Bark of Plumeria rubra Grown in Indonesia". International Congress on Natural Products Research, Park City, Utah, July, 1988. (Presented by L.B.S. Kardono).

Soejarto, D.D. and A.D. Kinghorn, "Correlation Between Field and Laboratory Data on Sweet-Tasting Plants". 30th Annual Meeting of the Society for Economic Botany, Knoxville, Tennessee, June, 1989.

Choi, Y.-H., R.A. Hussain, J.M. Pezzuto, A.D. Kinghorn, and J.F. Morton. "Four Highly Sweet Triterpene Glycosides from the Leaves of Abrus precatorius. 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August, 1989.

Kardono, L.B.S., S. Tsauri, K. Padmawinata, J.M. Pezzuto, and A.D. Kinghorn. "Novel Iridoids from the Bark of Plumeria rubra of Indonesian Origin". 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August, 1989. (Presented by L.B.S. Kardono).

Hussain, R.A., F. Fullas, J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn. "Articulin 2-acetate, a Cytotoxic Diterpene Constituent of Baccharis gaudichaudiana". 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August, 1989. (Presented by F. Fullas).

Tan, G.T., J.M. Pezzuto, and A.D. Kinghorn. "Screening of Natural Products for the Inhibition of Human Immunodeficiency Virus Reverse Transcriptase (HIV-RT): A Potential Target for the Treatment of AIDS". 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August, 1989. (Presented by G.T. Tan).

Fullas, F., Y.-H. Choi, A.D. Kinghorn, and N. Bunyapraphatsara. "Rapid Procedure for the Isolation of the Sweet Glycosides, Abrusosides A-D, from the Leaves of Abrus fruticulosus". 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August, 1989. (Presented by F. Fullas).

Jakinovich, Jr., W., Y.-H. Choi, and A.D. Kinghorn. "Use of Gerbil Electrophysiological and Behavioral Assays to Evaluate Plant Extracts for Sweetness". 30th Annual Meeting of the American Society of Pharmacognosy, San Juan, Puerto Rico, August, 1989.

Lotter, H., A.D. Kinghorn, S. Imre and H. Wagner. "Structure Elucidation of Three New Natural Products from Higher Plants and Marine Organisms with Biological Activity by X-ray Analysis". Phytochemical Society of Europe meeting, Lausanne, Switzerland, September, 1986. (Presented by H. Lotter).

Hussain, R.A., N.P.D. Nanayakkara, J.M. Pezzuto, D.D. Soejarto, A.D. Kinghorn and B.S. Chung. "Sugar Constituents of the Sweet Plants Hovenia dulcis, Inga spectabilis, Prosopis juliflora, and Thladianthia grosvenorii". 28th Annual Meeting of the Society for Economic Botany, Chicago, Illinois, June, 1987. (Presented by R.A. Hussain).

Croom, Jr., E.M., J.-M. Jai, S.-Q. Lui, D.D. Soejarto and A.D. Kinghorn. "Tian cha (Rubus suavissimus S. Lee): A Traditional Chinese Sweet Plant". 28th Annual Meeting of the Society for Economic Botany, Chicago, Illinois, June, 1987. (Co-presented by E.M. Croom).

Hussain, R.A., A.D. Kinghorn, and R.J. Molyneux. "Identification of the Alkaloid Constituents of Herbarium Specimens of Rothia trifoliata and R. hirsuta". 28th Annual Meeting of the American Society of Pharmacognosy, Kingston, Rhode Island, July 1987. (Presented by R.A. Hussain).

Hussain, R.A. and A.D. Kinghorn. "Positive and Negative Ion Chemical Ionization Mass Spectrometry of Steviol and Some Derivatives". 28th Annual Meeting of the American Society of Pharmacognosy, Kingston, Rhode Island, July, 1987. (Presented by R.A. Hussain).

Kim, J. and A.D. Kinghorn. "Structure Elucidation of (+)-Afzelechin-7-0-β-D-apioside, a Novel Bitter Principle of Polypodium glycyrrhiza, Using the Selective INEPT NMR Technique". 28th Annual Meeting of the American Society of Pharmacognosy, Kingston, Rhode Island, July, 1987. (Presented by J. Kim).

Choi, Y-H., J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "Further Activity-Guided Isolation Studies on Agrostistachys hookeri". 28th Annual Meeting of the Society of Pharmacognosy, Kingston, Rhode Island, July, 1987. (Presented by Y.-H. Choi).

Nanayakkara, N.P.D., R.A. Hussain, J.M. Pezzuto, D.D. Soejarto and A.D. Kinghorn. "Intensely Sweet Dihydroflavonol Derivatives". 28th Annual Meeting of the American Society of Pharmacognosy, Kingston, Rhode Island, July, 1987. (Presented by N.P.D. Nanayakkara).

Erdelmeier, C.A.J., P.A.S. Van Leeuwen and A.D. Kinghorn. "Separation of Phorbol Esters by Two-Dimensional TLC and Rapid Purification Using LPLC and Subsequent Reversed-Phase OPLC". 35th Annual Congress of the Gesellschaft fur Arzneipflanzenforschung, Leiden, The Netherlands, September, 1987. (Presented by C.A.J. Erdelmeier; Pharm. Weekbl. Sci. Ed., 9: 216, 1987).

Kim, J., J.M. Pezzuto, D.D. Soejarto, and A.D. Kinghorn. "Sweet Steroidal Glycosides from Rhizomes of Polypodium glycyrrhiza". International Congress on Natural Products Research, Park City, Utah, July, 1988.

Compadre, C.M., R.A. Hussain, R.L. Lopez de Compadre, J.M. Pezzuto and A.D. Kinghorn. "Structure-Activity Relationships for the Intensely Sweet Sesquiterpene Hernandulcin". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by C.M. Compadre).

Duh, C.-Y., J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "Cytotoxic Triterpene Esters from Stizophyllum riparium". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by C.-Y. Duh).

Hamburger, M., S.S. Handa, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Ostopanic Acid, a Cytotoxic Unsaturated Fatty Acid Derivative from Ostodes paniculata". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by M. Hamburger).

Choi, Y.-H., J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "Further Cytotoxic Constituents of Agrostistachys hookeri". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by Y.-H. Choi).

Duh, C.-Y., J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "Isolation, Characterization, and Mechanistic Evaluation of Stizophyllin, a New Cytotoxic Pregnane Derivative from Stizophylum riparium". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by C.-Y. Duh).

Erdelmeier, C.A.J., 1. Erdelmeier, A.D. Kinghorn and N.R. Farnsworth. "Overpressure Layer Chromatography (OPLC): Separations of Natural Products with Antineoplastic Activity". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by C.A.J. Erdelmeier).

Klocke, J.A., N.P.D. Nanayakkara, C.M. Compadre, R.A. Hussain, J.M. Pezzuto and A.D. Kinghorn. "Feeding Deterrent Effects on the Aphid, Schizaphis graminum, by Derivatives of the Sweet Compound, Stevioside". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by N.P.D. Nanayakkara).

Hussain, R.A., A.D. Kinghorn, M.F. Balandrin, C.H. Stirton and S.V. Evans. "Quinolizidine Alkaloid Profiles in Further Legume Species of the Tribe Sophoreae". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by R.A. Hussain).

Nanayakkara, N.P.D., A.D. Kinghorn and N.R. Farnsworth. "Sesquiterpenoid Constituents of Amanoa oblongifolia". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986. (Presented by N.P.D. Nanayakkara).

Choi, Y.-H., J. Kim, J.M. Pezzuto, A.D. Kinghorn, N.R. Farnsworth, H. Lotter and H. Wagner. "Agrostistachin, a Novel Casbane-Type Diterpene from Agrostistachys hookeri". 27th Annual Meeting of the American Society of Pharmacognosy, Ann Arbor, Michigan, July, 1986.

Nanayakkara, N.P.D., X. Fang, C.H. Phoebe, Jr., J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "4'-Demethyldeoxypodophyllotoxin, a Cytotoxic Constituent of Amanoa oblongfolia". 25th Annual Meeting of the American Society of Pharmacognosy, Austin, Texas, August, 1984. (Presented by N.P.D. Nanayakkara).

Duh, C.-Y., C.H. Phoebe, Jr., J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "Cytotoxic Constituents of Wikstroemia elliptica". 25th Annual Meeting of the American Society of Pharmacognosy, Austin, Texas, August, 1984. (Presented by C.-Y. Duh).

Che, C.T., X. Fang, C.H. Phoebe, Jr., A.D. Kinghorn, N.R. Farnsworth, B. Yellin and S.M. Hecht. "High-Field ^{1}H-NMR Characteristics of Some Cucurbitacins". 25th Annual Meeting of the American Society of Pharmacognosy, Austin, Texas, August, 1984. (Presented by C.T. Che).

Pezzuto, J.M., N.P.D. Nanayakkara, C.M. Compadre, S.M. Swanson, A.D. Kinghorn, T.M. Guenthner, L.K.T. Lam, V.L. Sparnins, and L.W. Wattenberg. "Evaluation of the Potential of Steviol (13-Hydroxy-ent-kaurenoic acid) and Related Diterpenes to Mediate Bacterial Mutagenesis and Induce Glutathione-S-transferase in Mice". 76th Annual Meeting of the American Association for Cancer Research, Houston, Texas, May, 1985. (Presented by J.M. Pezzuto; Proc. Am. Assoc. Cancer Res. 26:94, 1985).

Kinghorn, A.D., M.F. Balandrin, S.V. Evans and C.H. Stirton. "Quinolizidine Alkaloid Profiles of Legume Species of the Ormosia Group (tribe Sophoreae)." International Research Congress on Natural Products, Chapel Hill, North Carolina, July, 1985.

Fiebig, M., C.-Y. Duh, J.M. Pezzuto, A.D. Kinghorn and N.R. Farnsworth. "Cytotoxic Cardiac Glycosides of Streblus asper (Moraceae)." International Research Congress on Natural Products, Chapel Hill, North Carolina, July, 1985. (Presented by C.-Y. Duh).

Compadre, C.M., J.M. Pezzuto, N.P.D. Nanayakkara and A.D. Kinghorn. "Identification and Mutagenic Assessment of Steviol Metabolites." International Research Congress on Natural Products, Chapel Hill, North Carolina, July, 1985. (Presented by C.M. Compadre).

Marshall, G.T., L.-J. Lin, J.M. Pezzuto and A.D. Kinghorn. "Cytotoxic Activity of Some Diterpene Esters of the Tigliane, Daphnane, Ingenane, and Lathyrane Types." International Research Congress on Natural Products, Chapel Hill, North Carolina, July, 1985.

Pezzuto, J.M., R.J. Braun, N.P.D. Nanayakkara, C.M. Compadre and A.D. Kinghorn. "Further Studies on the Mutagenic Mechanism of Action of ent-13-Hydroxy-kaur-16-en-19-oic Acid (Steviol)." International Research Congress on Natural Products, Chapel Hill, North Carolina, July, 1985. (Presented by J.M. Pezzuto).

Makapugay, H.C. and A.D. Kinghorn. "Thladiantha grosvenorii: Source of an Intensely Sweet Triterpene Glycoside with Commercial Potential as a Sucrose Substitute." 36th Annual AIBS Meeting, Gainesville, Florida, August, 1985.

Hussain, R.A., A.D. Kinghorn and D.D. Soejarto. "Potential Sweetening Agents of Plant Origin: a Literature Search for Candidate Sweet Plants". 27th Annual Meeting of the Society for Economic Botany, New York, New York, June, 1986. (Presented by D.D. Soejarto).

Marshall, G.T. and A.D. Kinghorn. "New Phorbol Constituents of Croton Oil". 24th Annual Meeting of the Society for Economic Botany, Oxford, Ohio, June, 1983. (Presented by G.T. Marshall).

Arisawa, M., G.A. Cordell, A.D. Kinghorn and N.R. Farnsworth. "Ipomopsin - a New Biscoumarin from Ipomopsis aggregata (Polemoniaceae)". 24th Annual Meeting of the American Society of Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by G.A. Cordell).

Balandrin, M.F., N.S. Bhacca, R. Freeman and A.D. Kinghorn. "Two Dimensional FT-NMR Study of Acosminine, a New Legume Alkaloid with a Novel C20 Skeleton of Biogenetic Significance". 24th Annual Meeting of the American Society of Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by M.F. Balandrin).

Lin, L.-J. and A.D. Kinghorn. "Diterpene Ester constituents of the Latex of the Toxic Household Plant Euphorbia hermentiana". 24th Annual Meeting of the American Society oI Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by L.-J. Lin).

Compadre, C.M., N.P.D. Nanayakkara, J.M. Pezzuto and A.D. Kinghorn. "Mass Spectral Analysis of the Mutagenic Diterpene Steviol, the Aglycone of the Commercial Sweetening Agent, Stevioside, and Some of its Derivatives". 24th Annual Meeting of the American Society of Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by C.M. Compadre).

Nanayakkara, N.P.D., D.D. Soejarto, A.D. Kinghorn and S.K. Kamath. "Structure Determination of the Aglycone of the Sweet Triterpene Glycoside of Thladiantha grosvenori Fruits". 24th Annual Meeting of the American Society of Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by N.P.D. Nanayakkara).

Klocke, J.A., M. Arisawa, S.S. Handa, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Biological Activities of Quassinoids from Simaroubaceous Plants Against Two Species of Agricultural Pests". 24th Annual Meeting of the American Society of Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by J.A. Klocke).

Klocke, J.A., G.T. Marshall, L.-J. Lin and A.D. Kinghorn. "Biological Activity of Diterpenoid Esters from Plants of the Euphorbiaceae in Bioassays with the Cotton Pest Insect, Pectinophora gossypiella Saunders". 24th Annual Meeting of the American Society of Pharmacognosy, Oxford, Mississippi, July, 1983. (Presented by G.T. Marshall).

Compadre, C.M. and A.D. Kinghorn. "Ethnopharmacology of Lippia dulcis Trev." 25th Annual Meeting of the Society for Economic Botany, College Station, Texas, June, 1984. (Presented by C.M. Compadre).

Compadre, C.M. and A.D. Kinghorn. "Hernandulcin, a New Kind of Naturally Occurring Intensely Sweet Compound: Discovery, Structure Elucidation, and Synthesis." 25th Annual Meeting of the American Society of Pharmacognosy, Austin, Texas, August, 1984. (Presented by C.M. Compadre).

Compadre, C.M., J.M. Pezzuto, N.L. Katz, S.K. Kamath and A.D. Kinghorn. "Hernandulcin, a New Kind of Intensely Sweet Compound: Safety and Sensory Studies". 25th Annual Meeting of the American Society of Pharmacognosy, Austin, Texas, August, 1984.

Arisawa, M., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Further Antileukemic and Cytotoxic Constituents of Simaba multiflora." Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany, Boston, Massachusetts, July, 1981. (Presented by M. Arisawa).

Kim, I.-C. and A.D. Kinghorn. "A Reinvestigation of the Alkaloids of Lupinus sericeus." Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany, Boston, Massachusetts, July, 1981. (Presented by I.-C. Kim).

Kinghorn, A.D., N.P.D. Nanayakkhara, S. Yeh, D.D. Soejarto, P.J. Medon and S.K. Kamath. "Purification of Stevioside from Stevia rebaudiana by Droplet Counter-current Chromatography." Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany, Boston, Massachusetts, July, 1981.

Medon, P.J., J.M. Pezzuto, J.M. Hovanec-Brown, N.P.D. Nanayakkara, D.D. Soejarto, S.K. Kamath and A.D. Kinghorn. "Safety Assessment of Some Stevia rebaudiana Sweet Principles". FASEB 1982 Meeting, American Society of Pharmacology and Experimental Therapeutics Section, New Orleans, Louisiana, April, 1982. (Presented by P.J. Medon; Fed. Proc. 41: 1568, 1982.)

Badawi, M.M. S.S. Handa, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Antileukemic and Cytotoxic Constituents of Dirca occidentalis". 23rd Annual Meeting of the American Society of Pharmacognosy, Pittsburgh, Pennsylvania, August, 1982.

Hovanec-Brown, J.M., H.C. Makapugay, N.P.D. Nanayakkara, D.D. Soejarto, J.M. Pezzuto, P.J. Medon, A.D. Kinghorn and S.K. Kamath. "Sweet ent-Kaurene Glycosides from Stevia Leaf Herbarium Samples and their Biological Evaluation. 23rd Annual Meeting of the American Society of Pharmacognosy, Pittsburgh, Pennsylvania, August, 1982.

Marshall, G.T., L.-J. Lin and A.D. Kinghorn. "Droplet Counter-current Chromatography as a Technique for the Rapid Isolation of Tumor-Promoting Diterpene Esters from Plants of the Euphorbiaceae". 23rd Annual Meeting of the American Society of Pharmacognosy, Pittsburgh, Pennsylvania, August, 1982. (Presented by G.T. Marshall.)

Lin, L.-J. and A.D. Kinghorn. "Three New Ingenane Esters from Euphorbia canariensis Latex". 23rd Annual Meeting of the American Society of Pharmacognosy, Pittsburgh, Pennsylvania, August, 1982. (Presented by L.-J. Lin.)

Arisawa, M., N. Morita, J.M. Pezzuto, A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Anticancer Constituents of Ipomopsis aggregata (Polemoniaceae). 103rd Meeting of the Pharmaceutical Society of Japan, Tokyo, Japan, April, 1983. (Presented by M. Arisawa).

Kamath, S.K., M.L. Anderson, N.P.D. Nanayakkara, D.D. Soejarto and A.D. Kinghorn. Sensory Attributes of Some Stevia rebaudiana Sweet Principles". 5th Annual Meeting of the Association for Chemoreception Sciences, Sarasota, Florida, April, 1983.

Pezzuto, J.M., N.P.D. Nanayakkara and A.D. Kinghorn. "Steviol, the Aglycone of the Commercial Sweetening Agent Stevioside, is Mutagenic". 74th Annual Meeting of the American Association for Cancer Research, San Diego, California, May, 1983. (Presented by J.M. Pezzuto; Proc. Am. Assoc. Cancer Res., 24: 83, 1983).

ABSTRACTS - PAPERS PRESENTED AT NATIONAL/INTERNATIONAL MEETINGS

Evans, F.J. and A.D. Kinghorn. "A Screening Method for Euphorbia Cocarcinogenic Irritants." 110th British Pharmaceutical Conference, London, U.K., September, 1973. (J. Pharm. Pharmac. 25: 145-146P, 1973).

Soper, C.J., A.D. Kinghorn and F.J. Evans. "Preliminary Investigations on the Mode of Action of the Co-carcinogen A_1 Using Bacteria." 112th British Pharmaceutical Conference, Norwich, U.K., September, 1975. (Presented by C.J. Soper; J. Pharm. Pharmac. 27: 51P, 1975).

Seida, A.A., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "6α-Tigloyloxychaparrinone, a New Simaroubolide with Antileukemic and Cytotoxic Activity from Ailanthus integrifolia ssp. calycina." 18th Annual Meeting of the American Society of Pharmacognosy, Seattle, Washington, August, 1977. (Lloydia 40: 606-607, 1977).

Kinghorn, A.D. "Isolation of a Novel Irritant from Euphorbia tirucalli." First Joint Meeting of the American Society of Pharmacognosy and the Phytochemical Society of North America, Stillwater, Oklahoma, August, 1978. (Lloydia 41: 648-649, 1978).

Mahmoud, I.I., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Cytotoxic Drimane Sesquiterpenoids from Capsicodendron dinisii." 20th Annual Meeting of the American Society of Pharmacognosy, Purdue University, West Lafayette, Indiana, August, 1979. (J. Nat. Prod. 42: 681, 1979).

Kinghorn, A.D., M.A. Selim and S.J. Smolenski. "Combined Gas Chromatography-Mass Spectrometry of Lupinus Alkaloidal Toxins." 20th Annual Meeting of the American Society of Pharmacognosy, Purdue University, West Lafayette, Indiana, August, 1979. (J. Nat. Prod. 42: 688, 1979).

Balandrin, M.F. and A.D. Kinghorn. "Isolation of Sweetinine from Sweetia elegans." 20th Annual Meeting of the American Society of Pharmacognosy, Purdue University, West Lafayette, Indiana, August, 1979. (Presented by M.F. Balandrin; J. Nat. Prod., 42: 697, 1979).

Balandrin, M.F. and A.D. Kinghorn. "Pharmacognostic Investigation of Cascara Amarga." 21st Annual Meeting of the Society for Economic Botany, Bloomington, Indiana, June, 1980. (Presented by M.F. Balandrin).

Kinghorn, A.D., T.A. Hickey, S.M. Worobec and D.P. West. "Human Contact Dermatitis Evoked by the Latices of Synadenium grantii and Euphorbia hermentiana. 128th Annual Meeting of the American Pharmaceutical Association, St. Louis, Missouri, March, 1981.

Handa, S.S., A.D. Kinghorn, G.A. Cordell and N.R. Farnsworth. "Investigation of the Antileukemic and Cytotoxic Constituents of Soulamea soulameoides." Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany, Boston, Massachusetts, July, 1981. (Presented by S.S. Handa).

"Pharmacognosy: Drugs from Natural Sources", Colloquium lecture, Department of Pharmacy, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland, June 26, 1990.

"Sweetening Agents of Plant Origin", Institute of Pharmaceutical Biology, University of Munich, Munich, W. Germany, July 26, 1990.

"Potential of Higher Plants in the Discovery of New Anti-AIDS Agents", Symposium lecture, World Congress on AIDS, Bombay, India, December, 1990.

"Discovery of Plant Constituents with Anti-HIV Activity", College of Pharmacy, Seoul National University, Seoul, Korea, December 11, 1990.

"Highly Sweet Compounds from North and South American Medicinal Plants", Plenary lecture at the 21st Annual Convention of the Korean Society of Pharmacognosy, Seoul, Korea, December, 1990. (Kor. J. Pharmacog., 21:52-53, 1991).

"Anticancer and Anti-HIV Agents from Plants: Recent Progress", Genetic Engineering Center, Korean Institute of Science and Technology, Daeduk Science Town, Daejon, Korea, December 14, 1990.

"Novel Highly Sweet Compounds from Ethnobotanical Leads", Glaxo Group Research Limited, Greenford, Middlesex, England, May 1, 1991.

"Natural High-Potency Sweeteners: Recent Advances", Technical Center, Kraft General Foods, Inc., White Plains, New York, June 4, 1991.

"Plant-Derived Pharmaceuticals: Opportunities and Challenges", School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, September 16, 1991.

"Recent Progress in the Investigation of Potently Sweet Natural Products", Symposium lecture at the 43rd Southeast Regional Meeting of the American Chemical Society, Richmond, Virginia, November, 1991.

"The Search for Novel Highly Sweet Natural Products", Department of Pharmacodynamics, University of Illinois at Chicago, April 5, 1989.

"Highly Sweet Compounds of Natural Origin", XVI International Symposium on Natural Products Chemistry, ITESM, Monterrey Mexico, April 1989.

"Pharmacognosy: Drugs from Natural Sources", Symposium lecture at the 198th National Meeting of the American Chemical Society, Miami Beach, Florida, September, 1989.

"Drug Quality Control: Phytochemical Methods", Workshop on Assessment of Efficacy and Safety of Traditional Medicines, College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois, September 27, 1989.

"Plant Secondary Metabolites and Drug Discovery", College of Pharmacy, University of Texas, Austin, Texas, October 12, 1989.

"Pharmacognosy: Drugs from Natural Sources", Department of Botany, University of Texas, Austin, Texas, October 13, 1989.

"The Search for Antineoplastic and Sweetening Agents from Plants", Department of Botany, University of Texas, Austin, Texas, October 13, 1989.

"Natural High Potency Sweeteners: Some Recent Developments", Calorie Control Council 1989 Annual Meeting, Orlando, Florida, November 6, 1989.

"Plants as Sources of Biologically Active Molecules", H.H. Lehman College, City University of New York, Bronx, New York, November 15, 1989.

"Recent Studies on Biologically Active Compounds from Plants", Faculty of Pharmacy, Mansoura University, Mansoura, Egypt, January 21, 1990.

"Highly Sweet Substances and Other Biologically Active Plant Constituents", Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt, January 22, 1990.

"Antineoplastic Agents and Other Biologically Active Plant Constituents", Faculty of Pharmacy, University of Cairo, Cairo, Egypt, February 1, 1990.

"Thirty-Five Years of Achievement in Pharmacognosy Research by Norman R. Farnsworth, Norman R. Farnsworth Symposium on Natural Products Research, Chicago, Illinois, March 24, 1990. (With H.H.S. Fong and G.A. Cordell).

"Plant-Derived Sweetening Agents", Pharmacognosy-Phytochemistry Group, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland, May 9, 1990.

"Recent Studies on Cytotoxic and Sweetening Agents from Plants", Institute of Pharmacognosy and Phytochemistry, University of Lausanne, Lausanne, Switzerland, May 21, 1990.

"Anticancer Agents from Higher Plants", Pharmacognosy-Phytochemistry Group, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland, May 30, 1990.

"Drugs from Higher Plants: Recent Developments", Institute of Pharmacy, University of Berne, Berne, Switzerland, June 13, 1990.

"Noncariogenic Sweeteners from Plants", Department of Pharmacy, National University of Singapore, Singapore, November 7, 1985.

"Studies on Plant-Derived Anticancer Agents", Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand, November 12, 1985.

"Intensely Sweet Compounds of Natural Origin", Faculty of Science, Mahidol University, Bangkok, Thailand, November 12, 1985.

"The Search for Noncariogenic Sweetening Agents from Plants", Plenary lecture at the Second National Scientific Meeting on Phytotherapy and Phytopharmacy, Institut Teknologi Bandung, Bandung, Indonesia, December, 1985.

"The Phorbol Esters as Environmental Toxins", XIII International Symposium on Natural Products Chemistry, ITESM, Monterrey, Mexico, April, 1986.

"Applications of High-Field NMR Techniques and GC/MS to Phorbol Ester Structure Determination and Analysis", Symposium lecture at the 8th Rocky Mountain Regional Meeting of the American Chemical Society, Denver, Colorado, June, 1986. (With L.-J. Lin, G.T. Marshall, and R.A. Hussain). (J. Toxicol., Toxin Rev., 5:254, 1986).

"Approaches Toward the Discovery of New Sweet Molecules from Plants", Symposium lecture at the 21st Great Lakes Regional Meeting of the American Chemical Society, Chicago, Illinois, June, 1987.

"Biologically Active Compounds from Plants with Reputed Medicinal and Sweetening Properties", Plenary lecture at the 28th Annual Meeting of the American Society of Pharmacognosy, Kingston, Rhode Island, July, 1987.

"Antitumor Agents and Sweeteners of Vegetal Origin", University of Costa Rica, San Jose, Costa Rica, August 26, 1987. (Co-presented by D.D. Soejarto).

"The Search for Natural Sweeteners: Problems and Challenges", Workshop on Taste Modifiers, Sweeteners and the Mechanism of Sweet Taste, University of Wisconsin, Madison, Wisconsin, October 15, 1987.

"Intense Sweeteners and Antineoplastic Agents of Plant Origin", Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois, October 28, 1987.

"The Role of Traditional Medicine in Drug Discovery from Plants", The Japanese-United States Congress of Pharmaceutical Sciences, Honolulu, Hawaii, December, 1987. (With N.R. Farnsworth).

"Current Uses of Herbs in Medicine", Champaign-Urbana Herb Society, Urbana, Illinois, September 7, 1988.

"Potential Sucrose Substitutes of Plant Origin", International Conference on Sweeteners: Carbohydrate and Low Calorie, Los Angeles, California, September, 1988. (With D.D. Soejarto).

"Recent Studies on Some Intense Natural Sweeteners", Calorie Control Council 1988 Annual Meeting, Scottsdale, Arizona, November 15, 1988.

APPENDIX IV.

Credentials of Reviewers

CURRICULUM VITAE

Ryan James Huxtable

Birthplace and Date

England, September 20, 1943

Nationality

American

Marital Status

Married 1968, Wife Marion, No children

Degrees

B.Sc. 1964, Bristol University

Ph.D. 1968, Bristol University

Business Address

Department of Pharmacology
University of Arizona
Health Sciences Center
Tucson, Arizona 85724
(602) 626-6883

Home Address

6531 North Camino Libby
Tucson, Arizona 85718
(602) 797-0529

Positions

Professor, Department of Pharmacology, University of Arizona Health Sciences Center	7/79 - present
Associate Professor, Department of Pharmacology, University of Arizona Health Sciences Center	7/75 - 6/79
Assistant Professor, Department of Pharmacology, University of Arizona Medical Center.	10/70 - 6/75
Research Associate, Department of Biochemistry, Duke University Medical Center.	10/69 - 9/70
Research Associate, Department of Chemistry, University of Illinois.	9/68 - 10/69

Technical Officer, Mond Division, Imperial Chemical Industries, Runcorn, England.	1/68 - 8/68
Graduate Assistant, Department of Chemistry, Liverpool University.	7/66 - 12/67
Graduate Assistant, Department of Chemistry, Bristol University.	9/64 - 7/66

Visiting Professorships

Pfizer Travelling Professor, Clinical Research Institute, University of Montreal, 1974.

Visiting Professor, Clinical Research Institute, University of Montreal, 1977.

Visiting Professor, National Autonomous University of Mexico 1980.

Visiting Professor, University of Florence, Italy, 1981.

Visiting Scholar, Hastings Center (Institute of Society, Ethics and the Life Sciences), Hastings on Hudson, 1984.

Visiting Professor, University of Florence, Italy 1988.

Meetings Organized

First International Symposium on Taurine, Tucson 1975.

Second International Symposium on Taurine: Taurine in Neurological Disorders, Tucson 1977.

Workshop: Taurine in Epilepsy and Brain Development. Eleventh Annual Winter Conference on Brain Research, Keystone, Colorado 1978.

Symposium: Does Taurine Have a Function? American Society for Pharmacology and Experimental Therapeutics. Fall Meeting, Portland, Oregon 1979.

Symposium: A Western Problem: The Toxicology of Pyrrolizidine Alkaloids. Twenty-third Annual Meeting of the Western Pharmacology Society, Vancouver, Canada 1980.

International Symposium: Taurine: Questions and Answers, Mexico City 1980.

Editorial Committee, International Symposium on Sulfur Amino Acids: Biochemical and Medical Aspects, Tokyo 1982.

Editorial Committee, Twenty-first Congress of the Italian Pharmacological Society, Naples 1982.

Scientific Committee, Symposium: Taurine and Related Compounds, San Miniato, Italy 1986.

Organizing Committee, Second International Symposium on Guanidino Compounds, Shizuoka, Japan 1987.

Program Committee, Symposium on Taurine in Excitable Tissues: Biological and Clinical Aspects, Moguer, Spain 1989.

Symposium on Inhibitory Amino Acids, Tucson, Arizona 1990.

Other Invited Activities

Invited speaker: Symposium on oral contraceptives and high blood pressure. Gainsville, Florida, 1973.
Moderator: NIH Workshop on Lung Metabolism, Airlie, Virginia, 1975.
Panelist: Workshop on computer-assisted instruction. Eighteenth Annual Meeting of Western Pharmacology Society, Honolulu, 1975.
Panelist: Workshop on Taurine: Biosynthesis, Metabolism and Function. Ninth Annual Winter Conference on Brain Research, Keystone, Colorado, 1976.
Chairman: Pulmonary-Respiratory Pharmacology Session, FASEB, Chicago, 1977.
Invited speaker: Symposium on tansy ragwort. Corvallis, Oregon, 1979.
Chairman: Toxicology Session, Twenty-second Annual Western Pharmacology Meeting, Colorado Springs, 1979.
Invited speaker: Symposium on actions of taurine on excitable membranes. Philadelphia, Pennsylvania, 1979.
Invited speaker: Third international symposium on low molecular weight, sulfur-containing, natural products. Rome, Italy, 1979.
NIH Site Visitor: Comprehensive Epilepsy Program, University of Virginia Medical Center, 1979.
Chairman: Taurine and Carnitine Session, FASEB, Anaheim, 1980.
Chairman: Biochemical Pharmacology Session, ASPET, Rochester, Minn., 1980.
Invited participant: Workshop - Quebec Co-operative Study on Friedreich's Ataxia, Montebello, Quebec, 1980.
Invited speaker: Third Tarbox Parkinson's disease symposium, Lubbock, Texas, 1980.
Chairman: Taurine and Carnitine Session, FASEB, Atlanta, 1981.
Chairman: Environmental Toxicology Session, FASEB, Atlanta, 1981.
Program Organizer: Neurosciences Retreat, 'Teleology in the Neurosciences', University of Arizona, 1982.
Invited Speaker: Twenty-first Congress of the Italian Pharmacological Society, Naples, 1982.
Special Lecturer to Open Meeting: Role of Taurine in Cardiovascular System, International Symposium on Sulfur Amino Acids, Biochemical and Medical Aspects and Fifth Annual Meeting of Japanese Research Society on Sulfur Amino Acids, Tokyo, 1982.
Chairman: Symposium IV. International Symposium on Sulfur Amino Acids, Tokyo, 1982.
Chairman: Session on Physiological, Pharmacological and Toxicological aspects of Guanidino Compounds. International Symposium on Guanidino Compounds. Tokyo, 1983.
Invited speaker: Herbal Toxins. Third Annual Southwestern Poisons Symposium. Tucson, Arizona, 1983.
Invited Panelist: Workshop on, 'Is taurine a neurotransmitter?' Seventeenth Annual Winter Conference on Brain Research, Steamboat Springs, Colorado, 1984.
Invited speaker: Public health implications of pyrrolizidine alkaloids in foodstuffs. Twenty-seventh annual meeting of the Canadian Federation of Biological Societies, Saskatoon, Canada, 1984.
Chairman: Cellular Pharmacology Session. Ninth International Congress on Pharmacology, London, 1984.
Invited Speaker to close meeting: Symposium on taurine, Hanasaari, Finland, 1984.
Invited Speaker: First Annual Heart/Flinn Scientific Conference, Phoenix, Arizona, 1985.
Discussion Leader: Symposium on taurine and cellular development in nervous tissue, Sixth International Meeting of the International Society for Developmental Neurosciences, Queretaro, Mexico, 1986.
Chairman: Session on taurine: Nutritional and developmental aspects. Symposium on Taurine and Related Compounds, San Miniato, Italy, 1986.
Invited Consultant: World Health Organization International Program on Chemical Safety - Environmental Health Task Force on Pyrrolizidine Alkaloids, Tashkent, USSR, 1986.

NIH Site Visitor: Institute for Basic Research in Developmental Disabilities, Staten Island, 1987.
Chairman: Membranes and Transport Session, Thirtieth Annual Meeting, Western Pharmacology Society, Molokai, 1987.
Invited Speaker: Council for Tobacco Research Annual Meeting, Naples, Florida, 1987.
Chairman: Session on Physiological, Pharmacological and Toxicological Aspects of Guanidino Compounds, International Symposium on Guanidino Compounds in Biology and Medicine, Shizuoka, Japan, 1987.
Invited Speaker, Second Arizona Heart Association/Flinn Foundation Scientific Conference, Phoenix, Arizona, 1987.
Invited Speaker: International Symposium on 'Taurine and the Heart', 10th Annual Meeting of Japanese Research Society on Sulfur Amino Acids, Osaka, Japan, 1987.
Chairman: Ethnotoxicology Symposium: Thirty-first Annual Meeting, Western Pharmacology Society, Tucson, Arizona, 1988.
Invited Speaker: Ethnotoxicology Symposium - Pharmacology of Bites, Stings and Poisons, Thirty-first Annual Meeting, Western Pharmacology Society, Tucson, Arizona, 1988.
Co-Chairman: Minisymposium on Taurine, FASEB, Las Vegas, 1988.
Chairman: Session of taurine interaction with excitable membranes, Symposium on Taurine in Excitable Tissues: Biological and Clinical Aspects, Moguer, Spain, 1989.
Invited Speaker to conclude meeting: Symposium on Taurine in Excitable Tissues: Biological and Clinical Aspects, Moguer, Spain, 1989.
Invited Speaker: Taurine e Tessuti Eccitabili, University of Bari, Italy, 1989.
Invited Speaker: International Symposium on Drug Safety, Ottawa, Canada, 1989.
Invited Speaker: The Emil Aaltonen Symposium on the Healthy Brain, Tampere, Finland, 1990.
Nomenclature Committee, International Society for Toxinology, 1990-
Invited Lecturer: 64th Annual Meeting of the Japanese Pharmacology Society, Kobe, Japan, 1991.
Invited Lecturer: Canadian Society of Hospital Pharmacists, Toronto, Canada, 1991.
Invited Speaker: Symposium on "Perspectives on Food Safety: Natural Toxicants", 105th Annual International Meeting of the Association of Official Analytical Chemists, Phoenix, Arizona 1991.

Honors

Robert S. Flinn Established Investigator Award, The Flinn Foundation and the Arizona Heart Association, 1984-1987.

Editorships etc.

Chemical Abstracts Abstractor	1967 - 1972
Associate Editor, Life Sciences	1973 - 1975
Consulting Editor, Neurochemistry International	1980 - current
Literature Correspondent, Trends in Pharmacological Sciences	1981 - current
Editorial Board, Acta Neurologica	1981 - current
Editorial Council, Toxicon	1982 - current

Memberships

The Chemical Society (London)	1963 - 1975
American Chemical Society	1968 - 1975
American Associate for the Advancement of Science	1972 - 1984
American Association of University Professors	1971 - 1978

Western Pharmacology Society	1974 - current
American Society for Pharmacology and Experimental Therapeutics	1974 - current
The Hastings Center	1981 - 1990
International Society on Toxinology	1982 - current
Honorary Member, Japanese Society for Sulfur Amino Acid Research	1983 - 1987
International Society for Neurochemistry	1989 - current

Teaching Materials

Videotape: Cardiovascular Actions of Taurine (63 minutes). English original; translated into Japanese. Taisho Pharmaceutical Company, Tokyo, 1982. Copy in University of Arizona medical library.

Herbal teas and toxins: novel aspects of pyrrolizidine poisoning in the United States, and herbs along the western Mexican-American border. Syllabus materials. Third Annual Southwestern Poisons Symposium. Tucson, Arizona, 1983.

Audiotape: Dr's Interview - the significance of taurine and the toxicity of alkaloids in herbs, with accompanying Japanese/English texts. Published by Medical View Co., Ltd., Tokyo, Japan, 1991.

MALONE, MARVIN HERBERT, pharmacologist/toxicologist, educator, editor, researcher; b. Fairbury, Nebr., Apr. 2, 1930; s. Herbert August Frederick and Elizabeth Florinda (Torrey) M.; m. Shirley Ruth Cane, Dec. 21, 1952; children: Carla Margaret, Gayla Christa. B.S. in Pharmacy, U. Nebr., 1951, M.S. in Physiology and Pharmacology, 1953; Ph.D. in Pharmacology and Pharm. Scis., 1958; postgrad., Rutgers U., 1954-55. Asst. U. Nebr., Lincoln, 1951-53, 1956-58; research asst. Squibb Inst. Med. Research, New Brunswick, N.J., 1953-56; asst. prof. U. New Mex., Albuquerque, 1958-60; assoc. prof. U. Conn., Storrs, 1960-69; prof. pharmacology and toxicology U. of Pacific, Stockton, Calif., 1969-84, disting. prof., 1984-90, chair. Dept. Physiology and Pharmacology 1969-70, 1987-90, emeritus prof. 1990-date; head Wormwood Associates, consult. services 1990-date. Consultant: Drug Plant Labs., U. Wash., 1960-64; Research Pathology Assoc., 1967-70; Amazon Natural Drug Co., 1967-70; Atlas Chem. Industries Inc./ICI USA Inc., 1968-78; Northeastern U./SISA Inst. Research, 1977-82; Task Force on Plants for Fertility Regulation, WHO Spl. Program for Research, Devel. and Research Trn. in Human Reproduction, 1982-88. Governor's appt. State of Calif. Medical Therap. and Drug Advisory Comm., 1985-90. Author: Experiments in the Pharmaceutical Biological Sciences, 1973. Editorial bd: Jour. Natural Products: Lloydia, 1971-date; Jour. Ethnopharmacology, 1978-84. Editor: The Wormwood Review (literary), 1961-date; Pacific Information Service on Street-Drugs, 1971-78; Am. Jour. Pharm. Education, 1974-79; Pharmat, 1984-87; Jour. Ethnopharmacology, 1985-date. Contbr. 225 articles to profl. jours. Recipient: U. Pacific Distinction of Merit, 1980; Am. Assn. Colleges of Pharmacy plaque for outstanding services, 1980; Mead Johnson Labs. award, 1964; USPHS grantee, 1960-63, 1968-73; U.S. Army grantee, 1962-63; U. Conn. Res. Found. grantee, 1964-68. Fellow: Am. Found. Pharm. Educ., Am. Inst. Chemists; AAAS. Member: Am. Soc. Pharmacology and Exptl. Therap., Western Pharmacology Soc., Am. Soc. Pharmacognosy, International Soc. Ethnopharmacology (founding mem.), Am. Pharm. Assoc., Acad. Pharm. Scis. (sr.), Am. Assn. of Colleges of Pharmacy, Soc. Econ. Botany, Am. Assn. Univ. Prof., Sigma Xi, Rho Chi, Phi Lambda Upsilon, Phi Kappa Phi. Specialties: screening and assay of natural products from plants and higher fungi, biometrics, pharmacology of inflammation and antiinflammation, pharmacodynamics of psychotropic and autonomic agents, fertility regulation. Home/office: 722 Bedford Road, Stockton CA 95204-5214. Telephone: 209-466-8231.

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