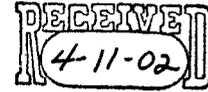




MARCO POLO TECHNOLOGIES, INC.
A Green Pharmaceutical Company

PREMARKETING NOTIFICATION

TO: Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling,
and Dietary Supplement (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835



DATE: March 31, 2002

Dear Sir/Madame:

HOMEGI BIOTECH INTERNATIONAL CORP., Taipei, Taiwan would like to notify FDA of its intent to market a dietary supplement, "**Sustotrong**" which contains new dietary ingredients, in the US market. It has authorized Dr. Yuan Lin of Marco Polo Technologies Inc. (Attachment 1) to be its representative who will handle matters regarding this notification. **Sustotrong** is a product of TCM Bio-Technology International. It is manufactured under contract by Sheng Chang Pharmaceutical Co. Ltd. and distributed by HOMEGI BIOTECH INTERNATIONAL CORP.

A. Name and complete address of Distributor

HOMEGI BIOTECH INTERNATIONAL CORP.
6th, Fl- 2, No. 560, Section 4, Chung-Hsiao E. Road
Shinyi Chiu, Taipei, Taiwan, 110
Republic of China

Authorized representative in the US

Dr. Yuan Lin
Marco Polo Technologies, Inc.
5900 Conway Road
Bethesda, MD 20817
301-897-5211 (phone); 301-530-5526 (fax)
e-mail: ylin60@yahoo.com

B. Name of product and dietary ingredients

Name of product: **Sustotrong**

Sustotrong is in capsule form. Each capsule contains 500 mg +/- 10%.

Each package contains 90 capsules. There is no structure/function claim on the label (Attachment 2—Package label).

Table 1 summarizes the ingredients in “Sustotrong”

Table 1. Botanical ingredients in Sustotrong

| Latin Name | Common Name | Part used | mg/tablet |
|---------------------------------|------------------|-----------|-----------|
| <i>Cordyceps sinensis</i> Sacc. | Cordyceps | Mycelium | 225 |
| <i>Triticum aestivum</i> L. | Common wheat | Seed | 175* |
| <i>Glycyrrhizae grabra</i> L. | Licorice root | Root | 10** |
| <i>Panax quinquefolius</i> L. | American ginseng | Root | 90* |

*Amount includes excipient (Starch) used during drying.

**Amount includes excipient (Dry powder of raw licorice) used during drying.

C. Description of dietary supplement

a. Level of each ingredient:

The final dry weight of each ingredient is listed in the last column of Table 1. Cordyceps was produced by fermentation in a biotechnologically aseptic environment. The other 3 ingredients were prepared by water extraction of raw materials (dried herbs) purchased from herbal market. The extract was filtered to remove particulate material and the supernatant was dried.

Table 2 provides the ratio from raw material to final ingredient.

Table 2. From raw material to final ingredients

| Ingredient | Concentration ratio* | Amount excipient used |
|------------------|----------------------|-----------------------|
| Cordyceps | 4.5 | No excipient added |
| Common Wheat | 4.6* | 32.5% of final weight |
| Licorice root | 3.7* | 33.3% of final weight |
| American ginseng | 3.2* | 18.9% of final weight |

*Concentration ratio was calculated as follows:

100 kg of common wheat was extracted and concentrated down to 14.5 kg. 7 kg of starch was added as an excipient to a final weight of 21.5 kg. Thus the concentration ratio is $100/21.5 = 4.6$. Similar calculations were performed for Licorice root and American ginseng. For cordyceps, mycelium was harvested and dried. The ratio is the wet weight/dry weight.

- b. Condition of use: For adults, take 2 capsules 2-3 times daily, one hour before meal.
- c. Evidence of safety: Three sets of safety data are included. One is the **contamination** levels of microorganisms, heavy metal and synthetic drugs in the final product **Sustotrong**; the second is the **dosage** of each ingredient recommended. In addition, the **acute toxicity** of the final product in mice is also included.

1. Contaminations: The manufacturing site at Sheng Chang Pharmaceutical Co., meets the GMP of Taiwan (Certificate attached, Attachment 3). Outmost care was taken at each step of the manufacturing process to avoid

contaminations.

1.1. Microbial and heavy metal contaminations: At the end of each batch production, the following tests were performed to ensure that the final product meets the contamination limits. Table 3 lists the test results of a representative batch of **Sustotrong** and the contamination limits for microorganisms, and heavy metals.

Table 3. Contamination limits for microorganisms, heavy metal and pesticides

| | Results of a representative batch | Upper allowable limits** |
|-----------------------|-----------------------------------|--------------------------|
| Microorganism* | | |
| Total plate count | 19000 cfu/g | 1x10 ⁵ cfu/g |
| Coliform | <3/g | 3/g |
| Yeast and Mold count | 20 col/g | 100 col/g |
| Heavy metal* | | |
| Arsenic | 0.4 ppm | - |
| Lead | <0.05 ppm | 0.5-1 ppm |
| Mercury | <0.05 ppm | 1 ppm |
| Cadmium | <0.05 ppm | 0.1 ppm |
| Selenium | 0.12 ppm | - |

*See Attachment 4 for test methods and results;

**the upper limits for microorganisms are those recommended by USDA for foods; the upper limits of heavy metals are those recommended by FDA as "Action Level for Poisonous or Deleterious Substances" for foods, 1998.

1.2 Contamination of synthetic chemical drugs: Attachment 5 is the chemical drug contamination test results of a representative batch of **Sustotrong**.

The tests show no detectable level of 28 drugs including steroids and agents commonly used for asthma and bronchial dilation.

Lots must pass above tests before releasing into the market.

2. Dosage of each ingredient recommended

Cordyceps:

Each 500mg capsule contains 225 mg of cordyceps. The serving size is 2 capsules each time to be taken 2-3 times daily.

In a similar product in the US market, Cordymax Cs-4, which was also produced by a fermentation process similar to ours, the recommended dosage by the Physician's Desk Reference is two 525 mg capsules three times daily (Attachment 6, PDF 1997). According to "Chinese Herbal Medicine: Materia Medica" by Bensky and Gamble, the toxicity level in animals is:

“IP injection of 5g/kg into mice caused no fatalities, but doses of 30-50 g/kg were universally fatal” (Attachment 6).

Thus the ingestion of the amount of Cordyceps in **Sustotrong** recommended in the label can be reasonably expected to be safe.

Common Wheat:

This ingredient meets the criteria that “it has been present in the food supply as an article used for food in a form in which the food has not been chemically altered”(21 CFR Part 190). Even though this ingredient has been extracted by water and concentrated, there is no chemical alteration occurring during the process. Thus this ingredient can be expected to be safe.

Licorice:

Each 500mg capsule contains 10 mg of Licorice. The serving size is 2 capsules each time to be taken 2-3 times daily.

Both licorice and licorice root extract are listed as OTC ingredients for miscellaneous internal use in FDA’s “OTC DRUG REVIEW INGREDIENT STATUS REPORT”, September 1, 1994. It is commonly used as an ingredient for candy. Thus it can be considered as an ingredient used in food. The extraction process (water extract) does not chemically alter the ingredient. The amount of 5-15 gram of root was recommended in German commission E monographs (Attachment 7). Based on the publication on the LD₅₀ in animal for oral use (14-18 g/kg in rat and mice, Attachment 7), and the fact that licorice is an ingredient used in food, we believe the ingestion of the amount of Licorice in **Sustotrong** recommended in the label can be reasonably expected to be safe.

American ginseng:

Each 500mg capsule contains 90 mg of American ginseng. The serving size is 2 capsules each time to be taken 2-3 times daily.

Ginseng is one of the most commonly used herbs in the US dietary supplement market.

Attachment 8 contains 2 publications (Kitts and Hu, 2000; Vogler et al., 1999) summarizing studies on the efficacy and safety of American ginseng. In mice, the LD₅₀ for ginseng ranges from 10-30 g/kg with a lethal oral dose of purified ginseng as high as 5g/kg body weight. In a 2-year human study, 14 out of 133 subjects were reported to experience side effects attributed to long-term exposure of ginseng when consumed at levels of up to 15g/day.

The amount of ginseng commonly suggested in Material Medica is 2-9 grams of ginseng each day (Attachment 8). The infusion is prepared by boiling of the ginseng root similar to the extraction process used in preparing **Sustotrong**. Each capsule contains 90 mg of extract with 18.9% excipient. In 2 capsules, the amount of ginseng extract is equivalent to $90 \times 71.1\% \times 3.2 \times 2 = 410$ mg raw ginseng (3.2 is the concentration ratio, Table 2).

Based on the historical use and animal toxicity studies, we believe the ingestion of the amount of American ginseng in **Sustotrong** recommended on

the label can be reasonably expected to be safe.

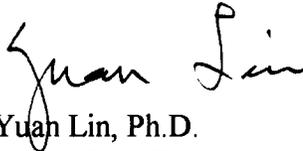
3. Acute toxicity test of final product, **Sustotrong**

The acute oral toxicity of **Sustotrong** was tested in mice at a single dose of 20g/kg (Attachment 9). No mortality was observed on 20 animals and was considered to have an acute oral LD₅₀ > 20g/kg.

To date, over a quarter million packages of **Sustotrong** have been sold in Taiwan and other Asian countries since 1997. This product is sold directly from our distributor with customer service direct line for proper usage and adverse reaction reporting. So far, we have not received any complaints of severe adverse reactions. Based on the ingredients used in this product and the stringent limits of contaminations, we believe **Sustotrong** when used at the amount recommended in the label can be reasonably expected to be safe.

Should you have any question concerning this product, please contact me at Marco Polo Technologies.

Sincerely Yours,



Yuan Lin, Ph.D.

Marco Polo Technologies, Inc.
5900 Conway Road, Bethesda, MD 20817
301-897-5211; 301-530-5526 (fax)
e-mail: ylin60@yahoo.com

Attachments:

1. Letter of authorization to Dr. Yuan Lin
Letter acknowledging the accuracy of the contents in the notification
2. Package Label
3. GMP Certification of Sheng Chang Pharmaceutical Co. Ltd.
4. Test report of microorganisms and heavy metals
5. Test report of the presence of chemical drugs
6. Recommended dosage for Cordyceps by PDR and animal toxicity test
7. Recommended dosage by German Commission E and LD₅₀ (Chinese Drug of Plant Origin) of Licorice
8. Recommended dose for American ginseng and publications on the safety of American ginseng
9. Acute oral toxicity test of **Sustotrong**



MARCO POLO TECHNOLOGIES, INC.
A Green Pharmaceutical Company

79967

March 31, 2002

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling,
and Dietary Supplement (HFS-820)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Sir/Madame:

Enclosed in this package are an original and two copies of a Premarketing Notification for a dietary supplement "Sustotrong" distributed by Homegi Biotech International Corp, Taiwan, Republic of China. Also included in each package are 9 attachments which contain information regarding the product's safety and a letter appointing me as their representative in the US.

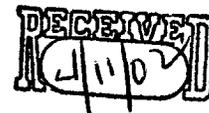
Should you have any questions please feel free to contact me.

Thank you very much.

Sincerely yours,

Yuan Lin, Ph.D.

RECEIVED



Attachment 1:

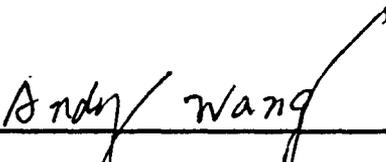
1. Letter of authorization to Dr. Yuan Lin
2. Letter acknowledging the accuracy of the contents in the notification



To Whom It May Concern;

This letter confirms that Dr. Yuan Lin of Marco Polo Technologies, has been retained as an Agent for TCM Bio-Technology International, Inc. and HomeGi Biotech International Corp., both are Taiwan based biotech company, with respect to all regulatory affairs pertaining to their desire to sell its herbal products in the US. Dr. Lin has been fully authorized to file dietary supplement notifications, new drug applications or any subsequent amendments deemed necessary and in the best interest for and on behalf of TCM Bio-Technology International, Inc. and HomeGi Biotech International Corp. in this undertaking. Dr. Lin will represent TCM Bio-Technology International, Inc. and HomeGi Biotech International Corp. in all regulatory matters to the Food & Drugs Administration.

Sincerely,

 2002. 1. 3.

Andy Wang - CEO, TCM Bio-Technology International, Inc.

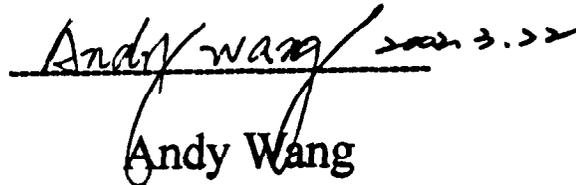


Yuan Lin, Ph.D.

Marco Polo Technologies, Inc.
5900 Conway Road, Bethesda, MD 20817

Dear Dr. Lin:

I acknowledge that the information disclosed in this FDA notification concerning Sustotrong is true and accurate.


Andy Wang

CEO

TCM Bio-Technology International, Inc.

Attachment 2: Package label

**Attachment 3: GMP Certification of Sheng
Chang Pharmaceutical Co. Ltd.**

**Translation of a “Letter of Notification” from the Bureau of Industry,
Ministry of Economic Affairs, Republic of China (ROC)**

Original letter to: Sheng Chang Pharmaceutical Co., LTD

Copies to: Office of Drug Administration, Department of Health, Executive Yuan,
ROC; Office of Building Administration, ROC; National Labs of Food
and drugs, Department of Health, Executive Yuan, ROC; Taipei
District Government

Identification Number: 48338

Content:

1. This is in response to your letter with ID # 573.
2. After our review, your Company is currently identified as “a GMP pharmaceutical manufacturing facility”. Your products include: Concentrated Chinese medicines in the form of powder, granules, tablets and capsules; Regular Chinese medicines in the form of herbs, cured herbs. Deleted from your previous registered forms are Regular Chinese medicine in the form of capsule, tablets, extracted powder and ointment.
3. This notice supercedes a previous notice ID#195.

Attachment 4:

Test report of microorganisms and heavy metals



SGS

SGS Hong Kong Ltd.
Retail & Supply Support Division

5F -7/F, Metropole Square, 2 On Yiu Street, Siu Lek Yuen, Shatin, N.T., Hong Kong

Tel : (852) 2364 2272 (Main)

Fax: (852) 2362 4647 (General Inquiry)

(852) 2363 3127 (Toys, Hardlines)

(852) 2334 2481 (Calibration)

(852) 2334 7827 / 2764 3276 (Textile & Footwear)

(852) 2766 3778 (Electrical) (852) 2603 7577 (Bio-Sciences)

(852) 2334 9085 (Chemical, Environmental, Food & Petroleum)

Test Report

No. 2000866/BS

Date : Mar 19 2001

Page 1 of 3

PERNZ WEY CO., LTD.*
5F-2., NO 112 CHUNG SHAN N. RD.
SEC. 2, TAIPEI
TAIWAN
R.O.C.

* PERNZ WEY CO. LTD. is the former name of HOMEGI BIOTECH
INTERNATIONAL CORP.

The content of this report is copied from report number 2000628/BS in full context.

Job No. : 1070573

Report on the submitted capsule sample identified by the client as 喜多壯冬蟲夏草.

| | | |
|----------------------------|---|---|
| Sample Description | : | 喜多壯冬蟲夏草 |
| Quantity | : | 27 packs (10 x capsules/pack) |
| SGS Sample No. | : | 1070573-101 |
| Manufacturer/Supplier | : | Sheng Chang Pharmaceutical Co., Ltd. |
| Country of Origin | : | Taiwan |
| Country of Destination | : | Hong Kong (South East Asia) |
| Sample Receiving Date | : | 13 October 2000 |
| Sample Receiving Condition | : | In sealed blister packs under ambient condition |
| Testing Period | : | 13 -23 October 2000 |

Test Requested, Test Methods and Test Results

Please refer to the following pages.

Signed for and on behalf of
SGS Hong Kong Ltd.



TAMMY CHENG
TECHNICAL DEPUTY DIRECTOR -BIO-SCIENCES SERVICES

This report is issued by the Company under its General Conditions printed overleaf. The issuance of this report does not exonerate buyers or sellers from exercising all their rights and discharging all their liabilities under the Contract of Sale. Stipulations to the contrary are not binding on the Company. The company's responsibility under this report is limited to proven negligence and will in no case be more than ten times the amount of the fees or commission. Except by special arrangement, the test items, will not be retained by the Company for more than three months. The results shown in this test report refer only to the sample(s) tested unless otherwise stated.
The test report cannot be reproduced, except in full, without prior written permission of the Company.

Member of the SGS Group (Société Générale de Surveillance)
See Reverse for Conditions

L1/08442



SGS

SGS Hong Kong Ltd. Retail & Supply Support Division

5F -7/F, Metropole Square, 2 On Yiu Street, Siu Lek Yuen, Shatin, N.T., Hong Kong

Tel : (852) 2364 2272 (Main)

Fax: (852) 2362 4647 (General Inquiry)

(852) 2363 3127 (Toys, Hardlines)

(852) 2334 2461 (Calibration)

(852) 2334 7827 / 2764 3276 (Textile & Footwear)

(852) 2766 3778 (Electrical) (852) 2603 7577 (Bio-Sciences)

(852) 2334 9085 (Chemical, Environmental, Food & Petroleum)

Test Report

No. 2000866/BS

Date : Mar 19 2001

Page 2 of 3

Test Requested

1. To determine Arsenic, Lead, Mercury, Cadmium, Chromium, Antimony and Tin content in the submitted sample.
2. To perform Total Plate Count, Coliform (MPN) and Yeast & Mould Count analyses on the submitted sample.

Test Method

1. Heavy Metal and Toxic Elements

The analyses were performed by the digestion of sample in acid mixture following with Inductively Coupled Argon Plasma Spectrometry measurement.

2. Total Plate Count and Coliform (MPN)

With reference to US FDA Bacteriological Analytical Manual, 8th edition, Revision A, 1998, Chapter 3 & 4 respectively.

3. Yeast & Mould Count

With reference to US FDA Bacteriological Analytical Manual, 8th edition, 1995, Chapter 18.

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See Reverse for Conditions

LI/U8441



SGS

SGS Hong Kong Ltd. Retail & Supply Support Division

5F -7/F, Metropole Square, 2 On Yiu Street, Siu Lek Yuen, Shatin, N.T., Hong Kong

Tel : (852) 2364 2272 (Main)

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(852) 2334 2461 (Calibration)

(852) 2334 7827 / 2764 3276 (Textile & Footwear)

(852) 2766 3776 (Electrical) (852) 2603 7577 (Bio-Sciences)

(852) 2334 9086 (Chemical, Environmental, Food & Petroleum)

Test Report

No. 2000866/BS

Date : Mar 19 2001

Page 3 of 3

Test Results

SGS Sample No. 1070573-101

喜多壯冬蟲夏草

Parameter

(1) Heavy Metal and Toxic Elements

| | |
|--|--------------------|
| Arsenic (as As ₂ O ₃) | 0.4 mg/kg (ppm) |
| Lead (Pb) | < 0.05 mg/kg (ppm) |
| Mercury (Hg) | < 0.05 mg/kg (ppm) |
| Cadmium (Cd) | < 0.05 mg/kg (ppm) |
| Chromium (Cr) | 1.7 mg/kg (ppm) |
| Antimony (Sb) | < 0.05 mg/kg (ppm) |
| Tin (Sn) | 0.1 mg/kg (ppm) |

(2) Microbiological Testing

| | |
|---------------------|-------------|
| Total Plate Count | 19000 cfu/g |
| Coliform (MPN) | < 3 /g |
| Yeast & Mould Count | 20 col/g |

Note : 1. For heavy metal and toxic elements analyses, results reported on powder inside capsule on an as received basis.

2. For microbiological analyses, results reported on sample on an as received basis.

3. cfu - colony forming unit

4. MPN - Most Probable Number

5. col - colony

Return Residue Sample

*** End of Report ***

This report is issued by the Company under its General Conditions printed overleaf. The issuance of this report does not exonerate buyers or sellers from exercising all their rights and discharging all their liabilities under the Contract of Sale. Stipulations to the contrary are not binding on the Company. The company's responsibility under this report is limited to proven negligence and will in no case be more than ten times the amount of the fee or commission. Except by special arrangement, the test items, will not be retained by the Company for more than three months. The results shown in this test report refer only to the sample(s) tested unless otherwise stated.

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Member of the SGS Group (Société Générale de Surveillance)

See Reverse for Conditions

L1/U044U

Attachment 5:

Test report of the presence of chemical drugs

Page 1. Report in Chinese

Page 2. English translation

Hwayo Tech & Lab Co., Ltd.

地址:243台北縣泰山鄉明德路三段423號4樓

郵政信箱:新莊郵政6-88號

電話:(02)29060887;傳真:(02)29060930

檢驗報告

委託單位/人: 大統醫事檢驗所/林光弘

樣品/委託編號: A890505-002-01/

樣品名稱/外觀: 喜多壯 / 褐色粉末

樣品重量: 6.26 g/瓶

檢驗項目: 中藥添加西藥

檢驗類別: 類固醇類, 支氣管擴張及氣喘類.

收件日期: 2000年5月5日

檢驗日期: 2000年5月5日

報告日期: 2000年5月10日

鑑別及檢驗方法:

A. 薄層層析法(Thin Layer Chromatography; TLC)及呈色法與對照標準品比對

1. 衛生署藥物食品檢驗局-中藥檢驗方法專輯(四)、(七)及(十)

2. 西藥成分薄層層析鑑別法及中藥製劑添加西藥成分檢驗分析方法 第一輯, 德國藥學博士 屈清亮 編著

3. 本公司研訂之標準操作方法(SOP)

B. 紫外光/可見光分光光譜儀(UV/Vis Spectrophotometer)

C. 原子吸收光譜儀(AA Spectrophotometer)

D. 化粧品衛生試驗法註解, 增訂第二版, 謝彭生, 1984-P204-205, 供學出版社

E. 其他

檢驗結果

檢驗結果: 未檢出下列西藥成分

Aminophylline 氨基非林

Bufexamac

Dexamethasone 氈月固醇

Diprophylline

Estriol

Hydrocortisone acetate 氈月固醇

Methyltestosterone 甲基氈月固醇

Phenylpropanolamine

Pseudoephedrine 偽麻黃素

Triamcinolone 類固醇

以下空白

Betamethasone

Chlorpheniramine maleate

Dextromethorphan

Ephedrine 麻黃素

Ethaverine

Methylephedrine 甲基麻黃素

Orphenadrine citrate

Prednisolone 類固醇

Testosterone propionate 男性賀爾蒙

Brompheniramine maleate 抗組織胺劑

Cortisone acetate 可的松

Diethylstilbestrol

Estradiol benzoate

Guaiacol glyceryl ether

Methylprednisolone

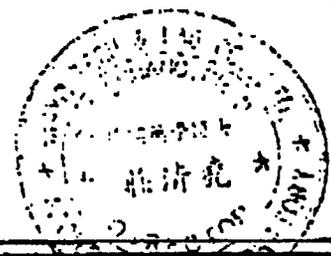
Papaverine

Prednisone

Theophylline

本公司產品
經檢驗

未檢出西藥成分



注意事項:

1. 本檢驗報告所列記錄僅對該送驗樣品負責, 如有疑問請於七日內向本公司查詢。

2. 本檢驗報告所載資料不得持具, 翻譯, 轉載或作為商業廣告, 出版物等宣傳推廣之用, 違者依法究辦。

3. 送驗樣品已清表完畢。

實驗室主任: 葉清亮 5/10

德國藥學博士

Translation of "Chemical Drugs Contamination"

Part one

Testing Lab and technician: Ewayo Tech & Lab Co. Ltd, K.H. Lin

Sample ID: A890505-002-01

Sample Name/ appearance: Sustotrong/ brown powder

Sample weight: 6.26 g/bottle

Test for: Chemical drugs in sample

Item to be tested: Steroids, agents for bronchial dilation and asthma

Receiving date: May 5, 2000

Test date: May 5, 2000

Reporting date: May 10, 2000

Part two

Methods of identification and testing

A. Thin Layer Chromatography, TLC: color development and comparison to standards

1. Manuals on Test Methods for Chinese Medicine, Vol 4, 7 and 10. National Labs of Food and Drugs, Department of Health
2. "TLC methods for detecting chemical drugs in Chinese medicine" by Dr. C.Y. Cheung
3. SOP for Chemical drug analysis, Ewayo Tech & Lab

B. UV/ Vis Spectrophotometer

C. AA Spectrophotometer

D. Testing of contaminations in cosmetics, 2nd edition, by P. S. Pang, 1984, pp 204-205

E. Others

Part three

Test results: there is no contamination of the following chemical drugs in the sample

| | | | | |
|------------------------|-------|--------------------------|-------|-------------------------|
| Aminophylline | 氨基菲林 | Betamethasone | | Brompheniramine maleate |
| Bufexamac | | Chlorpheniramine maleate | | Cortisone acetate 可的松 |
| Dexamethasone | 类固醇 | Dextromethorphan | | Diethylstilbestrol |
| Diprophylline | | Ephedrine | 麻黄素 | Estradiol benzoate |
| Estriol | 雌激素 | Ethaverine | | Guaiacol glyceryl ether |
| Hydrocortisone acetate | 皮质激素 | Methylephedrine | 甲基麻黄素 | Methylprednisolone |
| Methyltestosterone | 甲基睾丸酮 | Orphenadrine citrate | | Papaverine |
| Phenylpropanolamine | | Prednisolone | 类固醇 | Prednisone |
| Pseudoephedrine | 伪麻黄素 | Testosterone propionate | 男性荷尔蒙 | Theophylline |
| Triamcinolone | 类固醇 | | | |

Signature: C. Y. Chueng, Lab Chief, 5/10

Ph. D in Pharmacology

Attachment 6:

1. Recommended dosage of Cordyceps by the Physician's Desk Reference
2. Animal toxicity test-- Cordyceps

CHOLESTIN™
[kōlēs'tin]
600 mg capsules
Dietary Supplement

OTC

DESCRIPTION

CHOLESTIN is a natural, dietary supplement for use by adults concerned about maintaining healthy cholesterol levels, and should be used as part of a program including a healthy low fat diet and regular exercise. The key ingredients in CHOLESTIN have been used for centuries in China, and are produced today through modern fermentation techniques to assure consistent product quality and potency. In numerous foreign human clinical trials involving a significant number of human subjects, CHOLESTIN (including a more concentrated product) has been reported to have a positive influence on maintaining normal levels of blood lipids, including: human serum total cholesterol (TC) levels, serum triglyceride (TG) levels, low density lipoprotein cholesterol (LDL-C) levels, and high density lipoprotein (HDL-C) levels after continual supplementation for 4 to 8 weeks. These benefits were observed throughout the period of supplementation.

CHOLESTIN is prepared from premium rice fermented with *Saccharomyces purpureus* Went yeast and contains the natural fermentation by-products produced by the yeast. These natural by-products include a mixture of substances which resemble the known HMG-CoA reductase inhibitors, plus unsaturated fatty acids, amino acids and naturally-occurring red pigments.

CHOLESTIN capsules are supplied in 600 mg easy to swallow clear capsules for oral administration; the clear gelatin capsules are USP quality and designed to disintegrate within 30 minutes after ingestion.

RECOMMENDED USE

Dietary supplementation with CHOLESTIN is recommended for healthy adult males and post-menopausal women concerned about maintaining desirable cholesterol levels, and for whom their physician has determined that dietary supplementation rather than medical treatment is appropriate. CHOLESTIN is intended for use as part of a multiple cholesterol maintenance program that includes a healthy diet that is restricted in saturated fat and cholesterol, and other appropriate measures including regular exercise. CHOLESTIN is not recommended for treating a disease.

As a dietary supplement it is recommended that two 600 mg capsules of CHOLESTIN be taken twice per day (2 capsules shortly after the morning meal and 2 capsules with breakfast after the evening meal). Do not take more than 4 capsules in any 24 hour period.

WARNINGS

DO NOT USE this product if you are pregnant, can become pregnant, or are breast feeding.

CHOLESTIN is for adult use only. Cholestin is not to be used in anyone under 20 years of age.

DO NOT TAKE CHOLESTIN concurrently with any other drug without prior consultation with your doctor.

Ingredients in CHOLESTIN (HMG-CoA reductase inhibitors, e.g., lovastatin) have been associated with some rare but serious side effects, including serious diseases of the liver and skeletal muscle.

DO NOT TAKE CHOLESTIN if:

- you are at risk for liver disease, have active liver disease or any history of liver disease;
- you consume substantial amounts of alcohol (more than 3 drinks per day);
- you have a serious infection;
- you have undergone an organ transplantation;
- you have a serious disease or physical disorder or have recently undergone major surgery.

Immediately discontinue use of CHOLESTIN if you experience any unexplained muscle pain, tenderness or weakness, especially if accompanied by flu symptoms.

CHOLESTIN should be taken with a meal to minimize the risk of digestive tract discomfort.

Keep out of the reach of children.

TOXICITY

Tolerance limit of mice to CHOLESTIN is 16 grams per kilogram, which is equivalent to 533 times the level recommended for use as dietary supplement. Rats continuously force-fed CHOLESTIN for four months showed no abnormalities in all parameters and pathological examinations, and no differences to the control group.

In foreign clinical studies, no adverse effects were reported during the eight week study period. A small number of individuals reported slight discomfort in the digestive tract.

Further experience is obtained, no specific treatment of overdosage of CHOLESTIN can be recommended.

HOW SUPPLIED

CHOLESTIN 600 mg each are supplied in packages of 60 capsules. The deep purple-red powder is enclosed

in an easy-to-swallow clear gelatin capsule, and boxed in plastic-aluminum foil blister packs. CHOLESTIN can be purchased throughout the United States at major drug, grocery and mass merchandiser chains in the dietary supplement category; natural healthcare products section. Ask your Pharmacist for more details.

Storage: Store in a dry, cool place. Avoid excessive heat. Protect from light.

Shelf Life: Expiration date is imprinted on bottom of box and each blister pack.

The statement in the Physicians' Desk Reference regarding CHOLESTIN have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

EDUCATION MATERIALS

For more information and a booklet about CHOLESTIN and other PHARMANEX, INC products, call toll free 1-800-780-5180. For retail availability, or to talk to someone directly, please dial 1-805-582-9300 (FAX: 1-805-582-9301). For specific health-related questions about CHOLESTIN, call the Natural Products Hotline at 1-800-247-5169, 9:00 am to 5:00 pm, Mountain Time. Visit our website and access information directly from the Internet: <http://www.pharmanex.com>

Shown in Product Identification Guide, page 329

CORDYMAX Cs-4™

Cordyceps sinensis
[kord'yo-māk sē ēs fōr, kord'yo-seps sī-nēn-sis]
525 mg capsules
Dietary Supplement

OTC

DESCRIPTION

Cordyceps sinensis (Berk) Sacc, is one of the most valued natural products in Traditional Chinese Medicine and is prized as a potent tonic to promote general well-being. Cs-4 is an all natural fermentation product whereby the isolated principle active component of natural *Cordyceps sinensis*, the fungus *Paeecilomyces heptali* Chen, is grown on a proprietary blend of natural nutrients. In a biotechnologically aseptic environment, Pharmanex uses a proprietary deep-layer fermentation process that simulates the natural high altitude (greater than 14,000 feet) environment of the Tibetan plateau which is an optimal environment for the growth of *Cordyceps sinensis*.

Cs-4 most closely resembles the natural *Cordyceps* product in its scientifically-supported effects, and has an official monograph approved by the Chinese Ministry of Health distinguishing it as the first Traditional Chinese Medicine that has gone through pharmacology, toxicology and human studies in China. Cs-4 is standardized by HPLC method which ensures a potent and consistent product.

Cs-4 promotes a broad spectrum of health promoting functions, including the maintenance of normal, healthy lung function and general quality of life, including symptoms of tiredness and fatigue, by increased energizing effects and vigor. Cs-4 is not reported to stimulate the Central Nervous System or exhibit gastrointestinal tract effects.

CordyMax Cs-4 capsules are supplied in 525 mg easy-to-swallow clear gelatin capsules as a Dietary Supplement. The principle components of Cs-4 are adenosine, adenine, uracil, uridine, mannitol, beta-sitosterol, oligosaccharides, polysaccharides, eighteen common amino acids and the following vitamins and minerals: zinc, potassium, manganese, phosphorus, selenium, vitamin B-1, vitamin B-2 and vitamin E. Clear gelatin capsules are USP quality and are designed to disintegrate within 30 minutes after ingestion.

RECOMMENDED USE

As a dietary supplement: take two 525 mg capsules, three times per day with water and food.

USUAL DURATION OF USE

The effects of CordyMax Cs-4 are gradual; while mild effects are evident within a week, the most significant benefits take 3 to 6 weeks. Cs-4 has been taken as a daily dietary supplement by many people for years.

CONTRAINDICATIONS

None identified based on foreign human studies.

ADVERSE EFFECTS

Some subjects in human foreign studies showed a very slight sensation of thirst and one subject showed slight stomach discomfort; these effects were considered quite tolerable with the subjects. With the exception of one case of allergic skin reaction, no other adverse effects have been reported from clinicians and hospital records in China since the initial introduction of Cs-4 in 1989. Cs-4 has no reported CNS or GI effects.

WARNINGS

CordyMax Cs-4 has not been evaluated in children and should not be used by anyone under 18 years of age. CordyMax Cs-4 should not be used by pregnant or lactating women without advice from a physician.

OVERDOSAGE/TOXICITY

No incidence of toxic reaction has been reported. Acute toxicity studies: The LD₅₀ for oral administration to mice showed no death as 80 g/kg body weight.

HOW SUPPLIED

Capsules of CordyMax Cs-4™ 525 mg each are supplied in packages of 64 or 112 count. The dark brown powder is enclosed in an easy-to-swallow clear gelatin capsules, and boxed in plastic-aluminum foil blister packs. CordyMax Cs-4 can be purchased throughout the United States at major drug, grocery and discount stores in the dietary supplement category; natural products section. Ask the Pharmacist for more details.

Storage: Store in a dry, cool place. Avoid excessive heat. Protect from light.

Shelf Life: Expiration date is imprinted on bottom of box and each foil blister pack.

The statements in the Physicians' Desk Reference regarding CordyMax Cs-4 have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

EDUCATION MATERIALS

For more information and a booklet about CordyMax Cs-4 and other PHARMANEX INC. products, please call toll free at 1-800-780-5180. To speak with someone directly, call 1-805-582-9300 (FAX: 1-805-582-9301). For specific health-related questions about CordyMax Cs-4, call the Natural Products Hotline at 1-800-247-5169. Visit our website and access information directly from the Internet at <http://www.pharmanex.com>.

TEGREEN 97™

[te'grēn 97]
250 mg capsules
Dietary Supplement

OTC

DESCRIPTION

TEGREEN 97 is a green tea polyphenol extract derived from the leaves of the tea plant *Camellia sinensis*. The composition of TEGREEN 97 is similar to the natural profile of the fresh leaf, which is rich in the flavonol group of polyphenols known as catechins, as well as lesser amounts of proanthocyanidins, chlorophyll and caffeine. The major components of interest are the polyphenols, which have been scientifically-demonstrated to have superior free radical scavenging and antioxidant properties.

The term polyphenol denotes the presence of multiple rings. The major polyphenols in green tea, and the most significant of all tea components, are the catechins faction: epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), epigallocatechin gallate (EGCG), and proanthocyanidins. Of these factions, gallocatechins, especially ECG and EGCG appear to have the greatest capacity to quench free radicals.

The chemical composition of green tea leaves varies with climate, season, horticultural practices, and age of the leaf (position of the leaf on the harvested shoot). TEGREEN 97 is produced from high quality green tea leaves and processed through proprietary manufacturing methods to consistently provide a product with a high concentration of polyphenols (97%). Over two-thirds of the polyphenols in TEGREEN 97 are the important catechins faction as determined by HPLC method:

TEGREEN 97 Polyphenolic Profile

| | |
|-------------------|------------------------------------|
| Total polyphenols | ≥ 97% |
| Catechins faction | ≥ 65% |
| L-EGCG | ≥ 40% (-)-epigallocatechin gallate |
| L-ECG | ≥ 10% (-)-epicatechin gallate |
| L-EGC | ≥ 10% (-)-epigallocatechin |
| L-EC | ≥ 5% (-)-epicatechin |

Others: proanthocyanidines, lignans and phenolic acids
Minimal amounts of caffeine ≤ 2.5%

TEGREEN 97 capsules are supplied in 250 mg small, easy-to-swallow clear gelatin capsules as a Dietary Supplement for oral administration. The deep green color of TEGREEN 97's raw material result from the unique, mild extraction and purification process that allows for the retention of the natural chlorophyll found in fresh green tea leaves. Capsules are USP quality and are designed to disintegrate within 30 minutes after ingestion.

SCIENTIFIC SUPPORT

The ingestion of green tea polyphenols covers a very broad spectrum of functions promoting general well-being. In large scale epidemiological studies in Asia (involving more than 100,000 people for study periods up to 10 years), daily consumption of more than four cups of a green tea beverage has been associated with significant overall health maintenance of subjects, even after adjustments were made for age, smoking, alcohol consumption and relative body weight.



CHINESE
HERBAL
MEDICINE

Materia
Medica

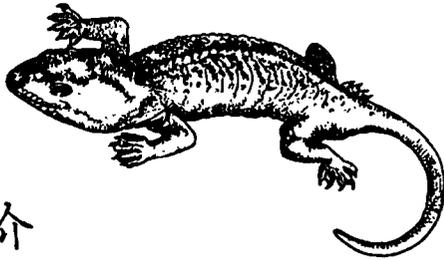
REVISED EDITION

Compiled and translated by
Dan Bensky and Andrew Gamble
with Ted Kaptchuk

Illustrations Adapted by
Lilian Lai Bensky

both the yin and the yang. It should be used in melted form and it is usually melted in any of the yellow wines. The dosage is 6-12g.

Cornu Cervi Degelatinatum (鹿角霜 *lù jiǎo shuāng*) is the dregs left over after boiling deer antler glue. Sweet and slightly warm, its ability to tonify and augment the essence and blood does not approach that of Cornu Cervi Parvum (*lu rong*). However it has a stronger retaining effect. Clinically, it is used mainly for cold deficient uterine bleeding and vaginal discharge. It can also be applied topically to stop bleeding. Please note that all three of these substances should not be used in patients with heat from yin deficiency.



蛤蚧

gē jiē

Pharmaceutical name: Gecko

Zoological name: *Gekko gekko*

Family: geckonidae

Where found: Shanxi as well as Yunnan, Guangdong, Guangxi, Jiangsu

When harvested: May to September

Japanese: *gōkai*

Korean: *hapkae*

English: gecko

Properties: salty, neutral

Channels entered: Lung, Kidney

Text in which first appeared: *Grandfather Lei's Discussion of Herb Preparation*

ACTIONS & INDICATIONS:

◆ Benefits the Kidneys and tonifies the Lungs: for Kidney and Lung deficiency, when the Kidney is unable to grasp the *qi*, manifesting as wheezing. Also used for consumptive cough or cough with blood-streaked sputum.

◆ Assists the Kidney yang and augments the essence and blood: for impotence, daybreak diarrhea, and urinary frequency from deficient Kidney yang.

MAJOR COMBINATIONS:

◆ With Radix Ginseng (*ren shen*), Semen Juglandis Regiae (*hu tao ren*), and Fructus Schisandrae Chinen-sis (*wu wei zi*) for cough and wheezing from deficient Lung and Kidneys, especially in cases where exhalation is much easier than inhalation. This is said to be a manifestation of the Kidneys' inability to grasp the Lung *qi*. This combination is also used for deficient

Kidney yang induced impotence, decreased sexual function, daybreak diarrhea, and frequent urination.

◆ With Cornu Cervi Parvum (*lu rong*) and Herba Epimedii (*yin yang huo*) for impotence due to Kidney yang deficiency.

◆ With Radix Rehmanniae Glutinosae (*sheng di huang*) for cough and wheezing accompanied by hoarseness or blood-streaked sputum from severe deficiency in the Lung and Kidneys.

◆ With Bulbus Fritillariae Cirrhosae (*chuan bei mu*) for chronic cough and wheezing resulting from Lung deficiency and the presence of phlegm heat.

CAUTIONS & CONTRAINDICATIONS:

◆ Contraindicated in patients with wheezing and coughing from either externally-contracted wind-cold or excess heat.

DOSAGE: 3-7g as a powder (in pills or powders); 9-15g in decoctions (the head and feet are usually not used in decoctions). Good quality is large, fat, intact, and includes the tail (as this is considered the most effective part).

MAJOR KNOWN INGREDIENTS: carnoside, carnitine, guanine, albumen

PHARMACOLOGICAL & CLINICAL RESEARCH:

◆ Hormonal effect: Alcohol extractions of Gecko (*ge jie*) prolonged the estrus periods and increased the weight of the sexual organs of mice, and induced estrus in oophorectomized mice. Preparations of Gecko (*ge jie*) had a weak or androgen-like effect on the prostate and testes of mice.

冬虫夏草

dōng chóng xià cǎo

Pharmaceutical name: Cordyceps Sinensis

Botanical name: *Cordyceps sinensis* (Berk.) Sacc. and (usually) the larval remains of *Hepialus varians* Staudinger.

Family: clavicipitaceae

Where grown: Sichuan, Qinghai, Guizhou, Yunnan, Tibet

When harvested: early summer when the fungus has emerged, but before the larval body has disintegrated

Alternate names: 虫草 *chóng cǎo*, 冬虫草 *dōng chóng cǎo*

Japanese: *tochūkasō*

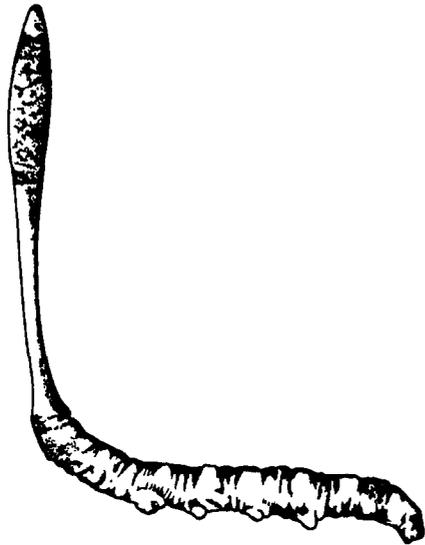
Korean: *tongch'unghach'o*

English: cordyceps (fungus and the carcass of the insect from which it grows), Chinese caterpillar fungus

Literal English translation: "winter bug summer herb"

Properties: sweet, warm

Channels entered: Lung, Kidney



Text in which first appeared: *Thoroughly Revised Materia Medica*

ACTIONS & INDICATIONS:

♦ Augments the Kidneys and tonifies the yang: for impotence and sore and weak lower back and lower extremities from Kidney yang deficiency.

♦ Tonifies the Kidney yang, augments the Lung yin, transforms phlegm, and stops bleeding: for chronic cough, wheezing from deficiency, or consumptive coughs with blood-streaked sputum. Because it tonifies both the yin and yang and is a very safe substance, it can be taken over a long period of time.

MAJOR COMBINATIONS:

♦ With Cortex Eucommiae Ulmoidis (*du zhong*), Herba Epimedii (*yin yang huo*), and Herba Cistanches Deserticolae (*rou cong rong*) for such symptoms as impotence, sore and weak lower back and lower extremities, and spermatorrhea associated with deficient Kidney yang.

♦ With Radix Adenophorae seu Glehniae (*sha shen*), Bulbus Fritillariae Cirrhosae (*chuan bei mu*), and Gelatinum Corii Asini (*e jiao*) for such symptoms as cough, wheezing, coughing up blood, and chest pain from deficient Lung yin.

♦ With duck, chicken, pork, or fish as a stew for weakness, dizziness, spontaneous sweating and other symptoms of debility and lowered resistance from a weakened protective qi.

CAUTIONS & CONTRAINDICATIONS:

- ♦ Use cautiously in exterior conditions.
- ♦ See Toxicity below.

DOSAGE: 4.5-12g. Good quality is intact with a short stick-like fungus and a bright yellow, fat, full, and round insect part with a yellowish white cross-section.

MAJOR KNOWN INGREDIENTS: cordycepic acid, cordycepin, glutamic acid, phenylalanine, proline,

histidine, valine, oxyvaline, arginine alanine, d-mannitol, vitamin B₁₂

PHARMACOLOGICAL & CLINICAL RESEARCH:

♦ Antibiotic effect: Very dilute solutions of Cordyceps Sinensis (*dong chong xia cao*) have an *in vitro* inhibitory effect against some of the tuberculosis bacilli. Preliminary studies also show an inhibitory effect *in vitro* on *Streptococcus pneumoniae*.

♦ Effect on muscle: Water extractions of Cordyceps Sinensis (*dong chong xia cao*) inhibit the contraction of smooth and cardiac muscle in many animal experiments. This herb causes bronchodilation of guinea pig lung specimens, inhibits contraction of intestinal and uterine specimens from rabbits, and inhibits heart specimens and *in situ* heart tissue from frogs.

TOXICITY: A relatively small dose of Cordyceps Sinensis (*dong chong xia cao*) can be tranquilizing and even hypnotic in animals. Intraperitoneal injection of 5 g/kg into mice caused no fatalities, but doses of 30-50 g/kg were universally fatal.



肉苁蓉

ròu cóng róng

Pharmaceutical name: Herba Cistanches Deserticolae

Botanical name: *Cistanche deserticola* Y. C. Ma. In some parts of China *C. salsa* (C. A. Mey.) G. Beck is used as this herb

Family: orobanchaceae

Where grown: Inner Mongolia, Tibet, Shaanxi, Gansu, Qinghai

When harvested: spring, just as the sprouts are emerging.

Alternate name: 淡大芸 *dàn dà yún*

Japanese: *nikujyūjō*

Attachment 7:

1. Recommended dosage of Licorice by the German Commission E Monographs
2. LD₅₀ of Licorice: Tang and Eisenbrand
“Chinese Drugs of Plant Origin”

THE COMPLETE GERMAN COMMISSION E MONOGRAPHS

THERAPEUTIC GUIDE TO HERBAL MEDICINES

*Developed by a Special Expert Committee of the German
Federal Institute for Drugs and Medical Devices*



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AMERICAN
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COUNCIL

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1998

Mode of Administration

Comminuted herb, herb powder, fluid extracts or dry extracts for teas and other galenical preparations. Ground herb and its preparations for oral use.

Note: Combinations with other sedative and/or carminative herbs may be beneficial.

Actions

Sedative
Carminative

Licorice root

Liquiritiae radix

Süßholzwurzel

Published May 15, 1985; Revised March 13, 1990,
April 19, 1991, and September 21, 1991

Name of Drug

Liquiritiae radix, licorice root.

Composition of Drug

Licorice root consists of unpeeled, dried roots and stolons of *Glycyrrhiza glabra* L. [Fam. Fabaceae], as well as their preparations in effective dosage. The unpeeled roots contain at least 4 percent glycyrrhizic acid and 25 percent water-soluble matter. Licorice root also consists of peeled, dried roots and stolons of *G. glabra* L. [Fam. Fabaceae], as well as their preparations in effective dosage. The peeled roots contain at least 20 percent water-soluble matter.

The root contains several flavonoids of flavanone and isoflavanone derivatives in addition to the potassium and calcium salts of the glycyrrhizic acid. It also contains phytosterols and coumarins.

Uses

For catarrhs of the upper respiratory tract and gastric/duodenal ulcers.

Contraindications

Cholestatic liver disorders, liver cirrhosis, hypertonia, hypokalemia, severe kidney insufficiency, pregnancy.

Side Effects

On prolonged use and with higher doses, mineralocorticoid effects may occur in the form of sodium and water retention and potassium loss, accompanied by hypertension, edema, and hypokalemia, and, in rare cases, myoglobinuria.

Interactions with Other Drugs

Potassium loss due to other drugs, e.g., thiazide diuretics, can be increased. With potassium loss, sensitivity to digitalis glycosides increases.

Dosage

Unless otherwise prescribed:

Average daily dosage:

About 5 - 15 g of root, equivalent to
200 - 600 mg of glycyrrhizin;

As *Succus liquiritiae*:

0.5 - 1 g for catarrhs of the upper
respiratory tract, 1.5 - 3 g for
gastric/duodenal ulcers;
equivalent preparations.

Mode of Administration

Powdered root, finely cut root or dry extracts for infusions, decoctions, liquid or solid dosage forms for internal use (*Succus liquiritiae*).

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JUN 15 1992

National Institutes of Health

W. Tang G. Eisenbrand

Chinese Drugs of Plant Origin

Chemistry, Pharmacology,
and Use in Traditional and Modern Medicine

With 41 Figures

Springer-Verlag
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Budapest

1992

74.1 Introduction

Gancao, Radix Glycyrrhizae, is the dry root and rhizome of *Glycyrrhiza uralensis* Fisch., *G. inflata* Bat. or *G. glabra* L. (Fabaceae), collected in the spring and fall. It is officially listed in the Chinese Pharmacopoeia. *Glycyrrhiza* root is one of the oldest traditional Chinese medicines and is used as a tonic, antiphlogistic, mucolytic, expectorant, analgesic for treatment of gastrointestinal and respiratory disorders, and also to alleviate the toxicity of some other drugs. However, it is reported not to be suitable in combined use with *Euphorbia kansui*, *E. pekinensis*, and *Daphne genkwa*.

Two galenic preparations of *Glycyrrhiza* root are listed in the Chinese Pharmacopoeia:

- Gancao Jingao, Extractum Glycyrrhizae, is the dry extract of *Glycyrrhiza* root, prepared by extracting the root with boiling water.
- Gancao Liujiangao, Extractum Glycyrrhizae liquidum, is the fluid extract of *Glycyrrhiza* root, prepared from the dry extract by adding concentrated ammonia solution, ethanol, and water.

The extract, as well as the fluid extract of *Glycyrrhiza* root, is used as an alleviative often in combination with mucolytic and expectorant preparations for the treatment of asthma, laryngitis, and bronchitis. Furthermore, they show an inhibitory effect on smooth muscle contraction in the gastrointestinal tract. Because of some desoxycorticosterone-like activity it could be used for treatment of chronic dysfunction of adrenal cortex. Successive administration of the extract or fluid extract of *Glycyrrhiza* root for a long time might cause side effects such as edema and hypertension, which disappear after withdrawal.

74.2 Chemical Constituents

The major constituent of the roots of *G. glabra*, *G. uralensis* [1], and *G. inflata* [2] is the triterpene saponin glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) with the sapogenin glycyrrhetic acid (glycyrrhetin, glycyrrhetic acid). Glycyrrhetic acid is a triterpene with an oleanan skeleton. Glycyrrhizin was first isolated from *Glycyrrhiza* root by Robiquet in 1809 [3]. After hydrolysis an aglycone and two molecules of sugar were obtained [4, 5]. Structure [6-8] and configuration [9] of the aglycone glycyrrhetic acid were shown to correspond to $3\beta,20\beta$ -3-hydroxy-11-oxo-olean-12-en-29-oic acid (74-1).

cortisol and aldosterone metabolisms, glycyrrhetic acid may delay clearance of corticosteroids and prolong their biological effects in the body [22]. Urinary cortisol excretion by normal volunteers given *Glycyrrhiza* extract was elevated [23].

Glycyrrhizin at a concentration of 8 mM completely inhibited growth and the cytopathic effects of vaccinia, herpes simplex type 1, Newcastle disease, and vesicular stomatitis viruses in cultures of human aneuploid HEP2 cells [24]. At the same concentration, glycyrrhizin inactivated herpes simplex virus irreversibly [24, 25]. The action mechanism of glycyrrhizin is probably based on the interaction with sensitive virus proteins at the virionic stage and during a later phase when these proteins are synthesized in host cells [24]. Antiviral activity of glycyrrhizin against varicella zoster virus in human embryonic fibroblast cells in vitro was also described and ascribed to inhibition of penetration, uncoating, or release of virus particle [26].

Glycyrrhizin was found completely to inhibit human immunodeficiency virus-induced plaque formation in MT-4 cells at the concentration of 0.5 mg/ml. The ID_{50} was 0.125 mg/ml. It also completely inhibited the human immunodeficiency virus-induced cytoplasmic effect and virus-specific antigen expression in MT-4 cells [27]. In comparison to glycyrrhizin, glycyrrhizin sulfate showed a stronger activity against human immunodeficiency virus [28].

Furthermore, glycyrrhizin showed an antiallergic activity [29]. It inhibited the passive cutaneous anaphylaxis response in rats and concentration dependently inhibited the contraction of rabbit ileum and guinea pig trachea induced by histamine, acetylcholine, or slow-reacting substances of anaphylaxis [30]. Ammonium glycyrrhizinate inhibited PGE_2 and $PGF_{2\alpha}$ formation by mouse lung and kidney in vivo and in vitro [31].

Glycyrrhizin and glycyrrhetic acid were able to prevent the development of experimental cirrhosis. In rats intoxicated with CCl_4 , the elevation of serum glutamic oxalacetic transaminase and the accumulation of triglyceride in the liver were decreased. Histopathological studies revealed that liver lesions in rats induced by CCl_4 were less severe in glycyrrhizin- and glycyrrhetic acid-treated animals than in controls. The liver glycogen level in treated rats was markedly decreased [32]. Glycyrrhizin significantly increased the weight of the spleen and thymus of mice and also increased the leukocyte count and the clearance rate of charcoal particles [33]. The therapeutic significance of glycyrrhizin alone or in combination with methionine against acute or chronic liver injury induced by CCL_4 or D-galactosamine was also described [34–36]. The combined use of glycyrrhizin and methionine had greater therapeutic effects than glycyrrhizin alone.

The LD_{50} values of a crude extract from *Glycyrrhiza* root containing about 50% glycyrrhizin were 1.4–1.7 g/kg by intraperitoneal and 14–18 g/kg by oral administration in rats and mice. Rats given orally a daily dose of 2.5 g/kg for 3 months showed decreased body weight gain, blood cell count, and thymus weight. Atrophic cortex and sporadic lymphofollicle formation were noted in the medulla of the thymus. All changes disappeared after discontinuation of *Glycyrrhiza* extract administration. Oral administration of 0.3–0.6 g/kg for 90 days in rats had no toxic effect [37]. Rats exposed to a dietary level of 4% ammonium salt of glycyrrhizin, corresponding to a daily dose of 2.6 g/kg for 4–6 months, produced hypertension, increase in relative weights of kidney, and a slight decrease in body weight and growth [38].

Glycyrrhizin was absorbed from rat small intestine according to an apparent first-order process. After oral administration of glycyrrhizin, glycyrrhetic acid was

Attachment 8:

1. Recommended dosage of American ginseng
Chinese Herbal Medicine—Materia Medica
Oriental Materia Medica
2. Kitts and Hu “ Efficacy and safety of
Ginseng”
3. Vogler et al. “The efficacy of Ginseng. A
systematic review of randomized clinical
trials”



CHINESE
HERBAL
MEDICINE

Materia
Medica

REVISED EDITION

Compiled and translated by
Dan Bensky and Andrew Gamble
with Ted Kaptchuk

Illustrations Adapted by
Lilian Lai Bensky

Alternate names: 南沙参 *nán shā shēn*,
大沙参 *dà shā shēn*, 空沙参 *kōng shā shēn*,
泡参 *pào shēn* (*Adenophora*); 北沙参 *běi shā shēn*,
辽沙参 *liáo shā shēn*, 条沙参 *tiáo shā shēn*,
银条参 *yín tiáo shēn* (*Glehnia*)

Japanese: *shajin*

Korean: *sasam*

English: adenophora or glehnia root

Literal English translation: "sand root"

Properties: sweet, cool; slightly bitter (*Adenophora*);
bland (*Glehnia*)

Channels entered: Lung, Stomach

Text in which first appeared: *Divine Husbandman's Classic of the Materia Medica*

ACTIONS & INDICATIONS:

◆ Moistens the Lungs and stops coughs: for dry, nonproductive cough due to Lung yin deficiency. Also for consumptive cough with blood in the sputum or hoarseness due to chronic cough.

◆ Nourishes the Stomach, generates fluids, and clears heat: used in the aftermath of a febrile disease or when yin deficiency causes dryness of the mouth or throat. Also for accompanying constipation.

◆ Moistens the exterior: for dry, itchy skin, especially when aggravated by cold, dry weather.

MAJOR COMBINATIONS:

◆ With Tuber *Ophiopogonis Japonici* (*mai men dong*) and Folium *Mori Albae* (*sang ye*) for chronic, dry, nonproductive cough with a marked reduction in fluids due to Lung yin deficiency. Also for thirst and dryness associated with Stomach yin deficiency.

◆ With Bulbus *Fritillariae Cirrhosae* (*chuan bei mu*) and Rhizoma *Anemarrhenae Asphodeloidis* (*zhi mu*) for dry cough with sputum that is difficult to expectorate due to Lung yin deficiency.

◆ With Herba *Dendrobii* (*shi hu*) and Radix *Rehmanniae Glutinosae* (*sheng di huang*) for thirst, dry throat and mouth, constipation, and/or low-grade fever due to Stomach yin deficiency in the aftermath of warm-febrile disease where the fluids have been injured.

◆ With Rhizoma *Polygonati Odorati* (*yu zhu*) and Tuber *Ophiopogonis Japonici* (*mai men dong*) for itching, especially when aggravated by dryness and cold as during the winter.

REMARKS: The differentiation of two types of Radix *Adenophorae* seu *Glehniae* (*sha shen*) was not clearly made until the 17th century in a work by Zhang Lu entitled, *Journey to the Origin of the Classic of Materia Medica*. At present two types are used: Radix *Adenophorae* (*nán sha shen*), or "southern sand root," and Radix *Glehniae Littoralis* (*běi sha shen*), or "northern sand root."

Most sources state that Radix *Adenophorae* is less potent in nourishing the yin and does not generate fluids, but is much better at stopping coughs. Nowadays if just *sha shen* is written in a prescription, Radix *Glehniae Littoralis* is usually given, although some sources indicate that Radix *Adenophorae* was more often used in ancient times.

CAUTIONS & CONTRAINDICATIONS: Contraindicated in cases with cough due to wind-cold, or Spleen cold from deficiency. According to some traditional sources, this herb antagonizes Radix *Aristolochiae Fangchi* (*fang ji*) and is incompatible with Rhizoma et Radix *Veratri* (*li lu*).

DOSAGE: 9-15g. Good quality is solid, long, and yellowish white in color. Radix *Adenophorae* is thicker and more pliable than Radix *Glehniae Littoralis*.

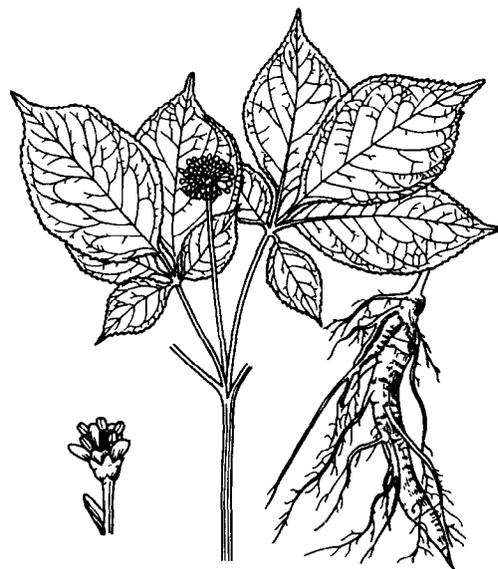
MAJOR KNOWN INGREDIENTS: alkaloids

PHARMACOLOGICAL & CLINICAL RESEARCH:

◆ Analgesic effect: Preparations of Radix *Adenophorae* seu *Glehniae* (*sha shen*) showed an analgesic effect for tooth extraction in rabbits.

◆ Cardiovascular effect: Dilute decoctions of Radix *Adenophorae* seu *Glehniae* (*sha shen*) showed a cardiotonic effect on frog heart specimens.

◆ Effect on temperature regulation: Alcohol extractions of Radix *Adenophorae* seu *Glehniae* (*sha shen*) lowered the fever induced by typhoid vaccination in rabbits. The herb also lowered the temperature of normal rabbits.



西洋参

xī yáng shēn

Pharmaceutical name: Radix *Panacis Quinquefolii*

Botanical name: *Panax quinquefolium* L.

Family: araliaceae

Where grown: northern United States and Canada; cultivated in France and northern China

When harvested: autumn (3 to 6-year-old plants)

Alternate names: 花旗参 huā qí shēn, 西参 xī shēn

Japanese: seiyōjin

Korean: sōyangsam

English: American ginseng root

Literal English translation: "western seas root"

Properties: sweet, slightly bitter, cold

Channels entered: Heart, Kidney, Lung

Text in which first appeared: *Omissions from the Grand Materia Medica*

ACTIONS & INDICATIONS:

◆ Benefits the qi, generates fluids, and nourishes the yin: for yin deficiency with heat signs, and chronic, unabating fever. Also for the aftermath of a febrile disease with such symptoms as weakness, irritability, and thirst.

◆ Nurtures the Lung yin and clears fire from the Lungs: for Lung yin deficiency with blazing fire such that the Lungs lose their clearing and dispersing functions. The primary manifestation is wheezing and coughing up blood-streaked sputum. Also for cough, coughing up blood, and loss of voice due to Lung yin deficiency.

MAJOR COMBINATIONS:

◆ With Gypsum (*shi gao*) and Rhizoma Anemarrhenae Asphodeloidis (*zhi mu*) for high fever, thirst, diarrhea, and dehydration associated with warm-febrile diseases in which both qi and fluids are injured. This combination is used for the yang brightness stage of the disease with concurrent qi deficiency.

◆ With Tuber Ophiopogonis Japonici (*mai men dong*), Gelatinum Corii Asini (*e jiao*), and Bulbus Fritillariae (*bei mu*) for wheezing and coughing up blood-streaked sputum from blazing fire due to Lung yin deficiency.

◆ Steamed with Arillus Euphoriae Longanae (*long yan rou*) for blood in the stool due to Intestinal heat.

REMARKS: This herb is not nearly as strong as Radix Ginseng (*ren shen*). It is best used for nourishing the yin.

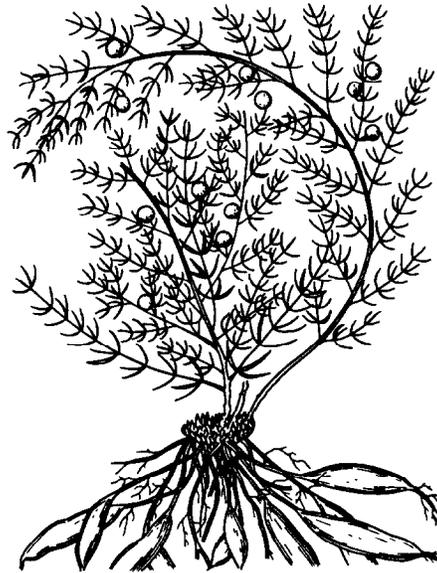
CAUTIONS & CONTRAINDICATIONS: Contraindicated in cases of damp-cold of the Stomach. According to some traditional sources, this herb is incompatible with Rhizoma et Radix Veratri (*li lu*).

DOSAGE: 2.4-9g. Often cooked separately from other herbs in double boiler. Good quality is hard, lightweight, and aromatic with dense striations on the surface.

MAJOR KNOWN INGREDIENTS: panaquilon, saponins

PHARMACOLOGICAL & CLINICAL RESEARCH:

◆ Central nervous system effect: In animal experiments preparations of Radix Panacis Quinquefolii (*xi yang shen*) had an inhibitory effect on the cerebral cortex, and moderately stimulated the subcortical centers.



天 门 冬

tiān mén dōng

Pharmaceutical name: Tuber Asparagi Cochinchinensis

Botanical name: *Asparagus cochinchinensis* (Lour.) Merr.

Family: liliaceae

Where grown: Guizhou, Sichuan, Guangxi, Hubei, Zhejiang, Jiangxi

When harvested: autumn or winter (preferred)

Alternate name: 天冬 tiān dōng

Japanese: tenmondō

Korean: ch'ōnmundong

English: asparagus tuber

Literal English translation: "lush winter aerial plant"

Properties: sweet, bitter, very cold

Channels entered: Kidney, Lung

Text in which first appeared: *Divine Husbandman's Classic of the Materia Medica*

ACTIONS & INDICATIONS:

◆ Nourishes Kidney yin and clears Lung heat: for yin deficiency with heat signs in the upper burner, typically dryness of the mouth. Also for dry Lung patterns with such signs as dry mouth and thick or blood-streaked sputum that is difficult to expectorate.

◆ Moistens the Lungs, nourishes the Kidneys, and generates fluids: for Lung and Kidney yin deficiency

ORIENTAL MATERIA MEDICA

a concise guide

簡明藥材學

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Traditional uses

Actions: Supplements *ch'i*, dispels lung heat, stimulates tissue regeneration, invigorates blood

Applications: Deficiency of *ch'i*, cough, asthma

Dosage

6 to 9 g.

*** 527. PANACIS QUINQUEFOLII RADIX**

(American Ginseng, *Hsi-Yang-Shen*, *Xi-Yang-Shen*, 西洋参)

Origins ③②

Hsi-yang-shen, also called *mei-kou-jen-shen* (美國人參), *yang-shen* (洋參), *hua-chi-shen* (花旗參), and *pao-shen* (泡參), first appeared in *Pen tsao kang mu shih i*. In 1714 a missionary, the Rev. Jartous, discussed it in an English journal; later, in 1716, the Rev. Lafiteau discovered this plant in southern Canada. It was then introduced into Southeast Asia via Hong Kong and Kuangtung province. It is the dried root of *Panax quinquefolium* L. of the Araliaceae family.



Panax quinquefolium ⑧

Essence and flavor

Bitter, sweet flavor; mild, cool property

Channels entered

The lung and the stomach meridians

Traditional uses

Actions: Nourishes yin, cleanses heat, increases salivation, supplements lungs, moistens and depresses fire

Applications: Heat symptom-complex, pulmonary tuberculosis, dry cough due to deficiency-heat

Chemical constituents ③②

Saponins 5%: ginsenoside-Rb₁, -Rg₁, -Rg₂, -Re, -Rb₂, -Rc, -Rd, -Ra, -Ro; panaquilon

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Pharmacology ③④②①

- (1) Sedative effect: Animal studies indicate that it tranquilizes the brain, but moderately stimulates the vital center.
- (2) Antifatigue effect: Ginsenoside Rg₁ helps to relieve fatigue.

Dosage

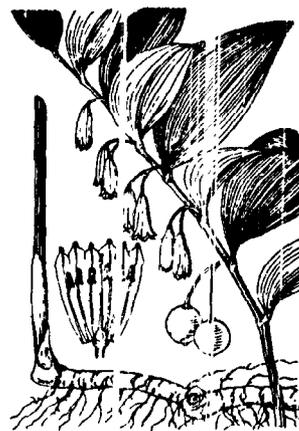
2 to 9 g.

*** 528. POLYGONATI OFFICINALIS RHIZOMA**(Solomon's Seal, *Yu-Chu*, *Yu-Zhu*, 玉竹)**Origins** ③②①

Yu-chu appears in *Shen nung pen tsao ching* as a high-grade drug under the name *nu-wei* (女萎). It was also called *wei-jai* (萎薺). *Yu-chu* derives its present name from nodes on its surface that look like bamboo nodes.

It is the dried rhizome of the following members of the Liliaceae family:

- (1) *Polygonatum officinale* ALL.
- (2) *P. inflatum* KOMAR.
- (3) *P. japonicum* MEISSN. [in Japan]

*Polygonatum officinale* ⑩**Essence and flavor**

Sweet flavor, mild, cold property

Channels entered

The lung and the stomach meridians

Traditional uses

Actions: Nourishes yin, moistens lungs, nourishes stomach, increases salivation

Applications: Impairment of yin due to febrile diseases, fidgets and sensation of heat, dryness in mouth and throat, dry cough due to lung heat

Chemical constituents ②

Convallamarin, convallarin, chelidonic acid, vitamin A, nicotinic acid

Efficacy and safety of ginseng

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Abstract

Ginseng (*Panax ginseng*, C.A. Meyer) has been a popular herbal remedy used in eastern Asian cultures for thousands of years. In North America, the ginseng species indigenous to both Canada and the United States (*Panax quinquefolium*) represents an important industry for both domestic and export markets. There are numerous theories and claims describing the efficacy of ginseng, which can combat stress, enhance both the central and immune systems and contribute towards maintaining optimal oxidative status against certain chronic disease states and aging. Risk issues concerning the safety of ginseng at recommended dosages are less prominent and scientifically based. While some epidemiological or clinical studies have reported indications of efficacy for specific health benefits or potential toxicity, there are an equal number of studies that provide contradictory evidence. This situation has led to questionable conclusions concerning specific health benefits or risks associated with ginseng. Recent advances in the development of standardized extracts for both *Panax ginseng* (G-115) and *Panax quinquefolius* (CNT-2000) have and will continue to assist in the assessment of efficacy and safety standards for ginseng products. This paper reviews the scientific literature and evidence for ginseng efficacy and safety derived mostly from *in vitro* and animal studies and places emphasis on the need for more randomized, double-blinded, placebo clinical studies that can provide unequivocal conclusions. An example of the efficacy and safety of ginseng is provided with the description of biological activity of a North American ginseng extract (NAGE), which includes illustrating mechanisms for antioxidant activity without prooxidant properties.

Keywords
Ginseng
Safety
Efficacy
Antioxidant activity

Ginseng is a perennial herb which is indigenous to Korea, China (*Panax ginseng* C.A. Meyer), Himalaya (*Panax pseudo-ginseng*), Vietnam (e.g. *Panax vietnamensis*), Japan (e.g. *Panax japonicus*) and North America (*Panax quinquefolium*). In North America, ginseng is grown commercially mainly in the Canadian provinces of British Columbia and Ontario. Wisconsin is the largest producer of North American ginseng in the United States. Ginseng, which is present in the Pharmacopoeas of China, UK and Germany, is regarded as a tonic with adaptogenic, stimulant and aphrodisiac properties¹⁻³. There is a considerable body of evidence to suggest that ginseng may also have important roles in maintaining oxidative status, by possessing both direct or indirect antioxidant functions. The validity of many of these claims should be determined by demonstrating the efficacy of the product, which supports the causal relationship between the bioactive constituent(s) and the proposed benefit. Closely associated with this evaluation process is the assurance that no adverse reactions exist with nutritional or toxicological endpoint parameters associated with consumption. In a recent

systematic review of the literature, Vogler *et al.*⁴ remarked on the paucity of controlled or randomized human studies that limits sound conclusions concerning the efficacy and safety of ginseng. The purpose of this paper is to review some of the clinical and epidemiological evidence concerning the efficacy and safety of ginseng, a common herb which can be found as an easily accessible food supplement. In addition, we have examined the *in vitro* chelating and reducing activity of a North American ginseng extract (NAGE; CNT-2000) and extended these experiments to establish standards of evidence for antioxidant activity associated with the inhibition of hydroxyl radical formation. Specific examples of biochemical activity related to the *in vitro* antioxidant properties of ginseng are presented to further demonstrate the potential efficacy of ginseng.

Ginseng composition

The recognized primary active components of ginseng are a group of 30 different triterpene saponins, also referred to as ginsenosides, which vary in content and relative

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proportions among different species of ginseng^{1,3}. Noting the differences in ginsenoside composition between North American and *Panax ginseng* C.A. Meyer ginsengs is important in assessing and interpreting efficacy and understanding safety. For example, traditionally recognized differences in pharmacological properties exist between different species of ginseng, as proposed by the ancient Asian concept of the complementary forces of *ying* and *yang*. In this example, it is the North American ginseng that provides the *ying*, or the cooling effect to offset stress, while *Panax ginseng* C.A. Meyer provides warmth, or the *yang* conditions to counter-balance stress. These apparent differences in cause and effect properties of ginseng may be related to the different composition of ginsenosides present in these two sources of ginseng. However, in addition to the bioactive ginsenosides, recent studies have also identified an acidic polysaccharide, referred to as 'Ginsan', with noted immunostimulatory activity^{5,6}. To alleviate the difficulty in assessing the bioactive properties of ginseng, relatively recent ginseng research has employed the use of standardized extracts of both *Panax ginseng* C.A. Meyer (G115, marketed as Ginsana) and North American ginseng (*Panax quinquefolium*, extract CNT-2000 from Chai-Na-Ta Corp., Langley, B.C.). These products hold the potential to enable improvements for assessing both quality control of ginseng products and efficacy of proposed activity from this herb. Of the numerous ginsenosides that have been identified from ginseng, six (namely Rb1, Re, Rc, Rd, Rb2 and Rg1) have been chosen for reference standards for ginseng products⁷.

It is noteworthy that although the *Panax quinquefolium* species is grown in both North America and Asia, pharmacological activity with specific organ systems has been reported to be stronger for the North American variety than the Asian counterpart⁸. Although the mechanisms underlying these differences in biological activity are not fully understood, subtle compositional differences are a likely explanation. Similar differences in bioactive properties have also been observed between cultivated and wild *Panax ginseng*⁹. Moreover, although the traditional source of ginsenoside from ginseng is the root, both the leaf and berry parts of this plant also contain significant quantities of ginsenoside¹⁰, thus adding to another potential variable in product source. In light of these facts, the employment of standardized extracts of ginseng with specified bioactive potential relative to known composition of active constituents will be the first step to assess efficacy and safety as well as ensuring optimal quality control of ginseng-based products. A good example of this is the proposal to include ginseng powder in multivitamin and mineral supplements for possible synergistic effect^{11,12}.

Ginseng metabolism

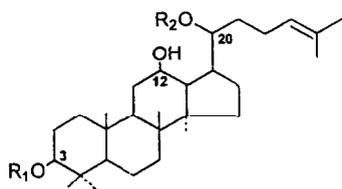
Central to the difficulties in explaining, in scientific terms, the underlying biochemical mechanisms for

various biological functions proposed for ginseng is the paucity of information concerning the absorption and metabolism of ginseng constituent(s) (e.g. primarily the ginsenosides, see Fig. 1). Pharmacokinetic studies conducted in rats have reported only 23% absorption of ginsenoside (Rb1) after a period of 2.5 h¹³. Very small recoveries of this ginsenoside were made in the liver (e.g. 0.25% dose) and heart (e.g. <0.1% dose), while the majority of the material was recovered in the small intestine. The bioavailability of bioactive ginseng constituents appears very limited, as evidenced by the low absorption rates for orally administered Rg1 (e.g. 0.1% dose) and Rg2 (e.g. 1.9% dose)¹⁴. Considering the fact that very little of the original ginsenoside material was recovered in the faecal matter (e.g. <1% dose), these results would appear to indicate that either metabolic or bacterial transformation of the parent ginsenoside constituents occurs in the small intestine. Support for this suggestion comes from studies conducted with bacteria collected from human intestines, which hydrolyse ginsenosides Rb1 and Rb2 to specific metabolites¹⁵, and which in turn are the likely forms absorbed from the intestine. Bacterial metabolites of ginseng have also been reported to have antigenotoxic properties¹⁶. The potential for the transformation of parent ginseng constituents to specific products of bacterial metabolism has made it difficult to directly associate various physiological effects noted for ginseng with standard pharmacokinetic parameters of specific ginsenoside absorption.

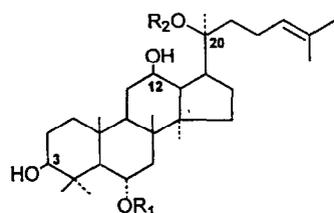
Adaptogenic effects of ginseng

Some adaptogenic effects of ginseng, initially reported by Brekhman and Dardymov¹⁷ are listed in Table 1, and probably involve changes in tissue oxygen uptake and transitory alterations in carbohydrate and lipid utilization. Perialisi *et al.*¹⁸ demonstrated increased oxygen uptake and related work load in normal subjects consuming ginseng. Earlier studies also reported increased oxygen uptake and transport in elderly subjects as well as enhanced energy levels in athletes¹⁹. These results are in agreement with other studies that have reported a dose-dependent *in vitro* increase in glucose uptake in brain tissue and associated decreases in lactate and pyruvate concentration ratios attributed to the presence of the standardized ginseng G115 extract²⁰. Reduced lactic acid metabolism by ginseng has also been reported in athletes undergoing intense exercise after consumption of 4% ginsenoside²¹. The enhancement of tissue glucose uptake and reduced production of anaerobic metabolic products have been explained by ginseng-related changes in tissue oxygen uptake.

The ergogenic effects of ginseng are less clearly observed in non-stressed experimental animal or human subjects, compared with counterparts which were challenged with an intense physical activity. For example,



$R_1=R_2=H$
20-(s)-protopanaxadiol



$R_1=R_2=H$
20-(s)-protopanaxatriol

Ra : R1=glucose-6→1-glucose-6→1-glucose
R2=glucose-3→1-glucose-3→1-glucose

Rb₁ : R1=glucose-2→1-glucose
R2=glucose-6→1-glucose

Rb₂ : R1=glucose-2→1-glucose
R2=glucose-6→1-arabnose(pyr)

Rb₃ : R1=glucose-2→1-glucose
R2=glucose-6→1-xylose

Rc : R1=glucose-2→1-glucose
R2=glucose-6→1-arabnose (fur)

Rd : R1=glucose-2→1-glucose
R2=glucose

Re : R1=glucose-2→1-rhamnose
R2=glucose

Rf : R1=glucose-2→1-glucose
R2=H

Rg₁ : R1=glucose
R2=glucose

Rg₂ : R1=glucose-2→1-glucose
R2=H

Fig. 1 Characteristic ginsenosides present in Asian and North American ginseng

studies designed to evaluate exercise performance due to ginseng supplementation have reported a marked stimulating effect of ginseng on carbohydrate and lipid mobilization and utilization²². Rats given a ginseng extract devoid of ginsenosides Rb₁ and Rg₁, prior to exercise, exhibited a preference for utilization of free fatty acids, thereby sparing glucose and glycogen levels. As a result of these animal studies, ginseng has recently been evaluated in human subjects for efficacy in numerous exercise performance studies²²⁻²⁸ and incorporated in sports drinks to enhance athletic performance²³. Many of these studies, however, have questioned the proposed ergogenic effect of ginseng²⁴⁻²⁶. In a clinical study comprising two dosage treatment groups receiving 8 and 16 mg kg⁻¹ body weight of both a placebo and ginseng before an intense cycling exercise, no effect of ginseng ingestion for a 1 week period was observed in enhanced physical endurance compared with placebo treatment²⁵. A randomized, double-blinded, placebo controlled study of healthy men receiving 200 and 400 mg day⁻¹ of a *Panax ginseng* extract (G115) drew similar conclusions. The study showed no effect on oxygen consumption,

respiratory exchange ratio, blood lactic acid and perceived exertion in men receiving ginseng²⁶. Similar results have been reported in healthy adult females using a randomized, double-blind placebo-controlled experimental design²⁵.

The fact that many of the metabolic effects attributed to ginseng relate to adaptation of homeostatic mechanisms resulting from exposure to stress, suggests some interaction between ginseng constituents and endocrine activity (Table 1). Ginseng has been reported to bring about changes in circulating levels of adrenocorticotrophin hormone²⁷ and corticosterone concentrations²⁸. Specifically, two ginsenosides, Rb₁ and Rg₁, have been reported to possess glucocorticosteroid activity due to a tendency to behave as functional ligands to the glucocorticoid receptor²⁹. The tendency of ginseng to exhibit apparent ergogenic, or non-specific resistant effects, is possibly due to the increased adrenal responsiveness afforded by ginseng constituents which ultimately enhances the activity of the pituitary-adrenal axis.

Significant increases in plasma corticosterone attributed to both intraperitoneal and oral administration of ginseng

Table 1 Reported metabolic and adaptogenic effects of ginseng

| | | Observed effect | Reference |
|---------------------------|--|-----------------|-----------|
| Physiological system | | | |
| Metabolic | | | |
| | Enhanced oxygen uptake | | 19 |
| | Enhanced cellular glucose uptake | | 20,21 |
| | No effect on plasma cholesterol level | | 24 |
| | Activates DNA polymerase | | 79 |
| | Stimulatory effect on brain neuronal activity | | 9 |
| | Lowers blood glucose in non-insulin diabetic patients | | 31,32 |
| | No ergogenic effects | | 24-26 |
| Endocrine | | | |
| | Enhanced adrenocorticotrophin secretion | | 27,28 |
| | Rb1, Rc, Rd-induced increase in plasma corticosterone | | 28,30 |
| | Reduced Ach-evoked catecholamine release | | 80 |
| Immune | | | |
| | Enhanced function of peripheral blood mononuclear cells in immune compromised subjects | | 81 |
| | Rg1-induced increase in T-helper cells | | 82 |
| | T-cell and macrophage cytokine induction | | 6 |
| | Rb1-induced reduction of leukotriene release | | 83 |
| | Immunostimulatory activity in the aged | | 84,85 |
| Chronic disease condition | | | |
| Cancer | | | |
| | Anti-neoplastic immunostimulatory activity | | 5 |
| | Specific anti-mutagenic and anti-tumour activity | | 86-91* |
| | Protection from radiation-induced DNA damage | | 92 |
| | Rb2-induced inhibition of tumour metastasis | | 93 |
| | Epidemiological evidence of protection against cancer | | 94,95 |
| | Enhanced recovery of cardiac ischaemia injury | | 48,96 |
| Cardiovascular | | | |
| | Enhanced recovery of brain ischaemia injury | | 41 |
| | Inhibition of platelet aggregation | | 97 |
| | Protection by ginsenoside-induced nitric oxide release | | 44,98 |

* Ref. 87 - no interference with therapeutic cancer agents.

have also been shown to parallel increases in plasma glucose and decrease plasma immunoreactive insulin³⁰. Other studies have reported ginseng constituents to lower blood glucose and stimulate insulin release in diabetic animals³¹. Similar findings have been reported in non-insulin-dependent subjects administered 100 mg and 200 mg ginseng in a random study that continued for 8 weeks³². Reduced fasting blood glucose corresponded to an increased physical activity and body weight reduction. Future clinical studies are needed with accompanying information on the specific ginsenoside content to confirm efficacy and safety of the proposed adaptogenic properties of ginseng.

Ginseng and oxidative status

The abundance of studies that have shown a strong association between ginseng intake and increased levels of activated oxygen species in various pathological states, or during natural processes such as exercise³³, demonstrates the importance of antioxidant mechanisms which function to preserve oxidative status. The oxidative damage to carbohydrates, proteins, nucleic acids and lipids resulting from contact with free radicals is believed to be the source of early detrimental cellular changes that influence the aetiology of chronic disease (e.g. cancer, atherosclerosis) and aging. The oxidative status of the

individual is balanced by the activity of both non-enzymatic antioxidant compounds (e.g. tocopherols, β -carotene, glutathione) and antioxidant tissue enzymes (e.g. superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px)), which together prevent reactive oxygen species formation, or work to mitigate the damage caused to cells by various sources of free radicals³³.

The role of ginseng constituents in supporting antioxidant defence mechanisms has also been shown to involve direct stimulation of cell defence mechanisms (Table 2). Prolonged administration of standardized ginseng G15 extract to rats reduces oxidative stress in certain tissues by altering specific antioxidant enzyme activities that are required to eliminate free radicals, thus reducing specific end-products of tissue peroxidation reactions³⁴⁻³⁶. Common to these studies has been the demonstration of a dose-dependent, ginseng-induced increase in GSH-P_x activity and an associated decrease in tissue malonaldehyde. This effect is particularly evident in stress-induced states, such as that reported with the intense exercising of rats that resulted in both an increase in cytosolic and mitochondrial GSH-P_x and SOD activities³⁶. Marked protective effects of ginseng against chemical induced hepatotoxicity has also been reported³⁷, thus demonstrating a role for ginseng in protecting against xenobiotic toxin-induced peroxidation

Table 2 Standards of evidence for ginseng antioxidant activity

| Evidence | Reference |
|---|-----------|
| <i>In vitro model mechanisms</i> | |
| Inhibition of Fenton reaction induced radicals | |
| (a) Fe ²⁺ -cysteine induced peroxidation of cultured liver, brain microsomal assay | 99 |
| (b) Membrane fatty acid peroxidation assay | 53 |
| (c) Site-specific deoxyribose degradation assay | 54 |
| (d) DNA scission assay | 54,58 |
| (e) Electron spin resonance analysis | 56 |
| <i>In vivo mechanisms</i> | |
| Tissue antioxidant enzyme activity | |
| (a) Reduced hepatic GSH-Px activity and MDA levels | 34 |
| (b) Reduced hepatic GSH-Px and SOD activities (exercised) | 36 |
| (c) Rb1 & Rb2-induced increased hepatic GSH-Px activity | 100 |
| (d) Rc-induced decrease in Cu/Zn SOD activity | 100 |
| (e) Rh2-induced increase in catalase activity | 100 |
| (f) Nitric oxide-like activity in pre-contracted aortic rings | 48 |
| (g) Rb2 induced expression of Cu/Zn SOD1 gene | 101 |

reactions. Specific ginsenosides have also been shown to protect against cellular toxicity induced from oxygen and lipid derived free radicals in dogs with haemorrhagic shock³⁸, and characterized in a ferrous/cysteine peroxide induction model system using hepatic microsomes³⁹. The affinity of Rb1 and Rg1, in particular, to scavenge reactive oxygen species in hepatic and brain microsome preparations exposed to Fenton type oxidation reactants, has been reported to occur at ginsenoside concentrations of 10⁻³ to 10⁻⁴ M³⁹. These same workers observed significant reductions (28%) in malonaldehyde and associated increases in GSH-Px (96.4%) and CAT (47%) after administering 50 mg kg⁻¹ day⁻¹ Rb1 to rats.

The protection against oxidative stress afforded by ginseng consumption has also been associated with the regulation of Cu/Zn SOD at the molecular level. Kim and coworkers⁴⁰ demonstrated that both total saponins and panaxatriol were ineffective at inducing SOD levels, whereas Rb2 triggered a specific induction of SOD transcription. The interaction of Rb2 with an activator protein (AP2) in a promoter region of the SOD gene resulted in the induction mechanism for antioxidant enzyme activity. Using a heterotropic heart transplantation model for myocardial ischaemia and re-perfusion, Liu and Xiao¹ observed that ginsenosides both stimulated myocardial SOD activity and reduced malonaldehyde, a product of lipid peroxidation. Similar antioxidant properties have also been reported in studies using ischaemic re-perfusion injury in the rat brain⁴¹. Additional evidence of an indirect *in vivo* antioxidant role for ginseng has come from studies that proposed the preservation of tissue SOD activity, resulting from the consequence of ginseng-induced stimulation of nitric oxide production^{2,42}. The tendency of ginseng to prevent the effects of oxygen free radical induced injury by promoting nitric oxide release has been confirmed in studies using pulmonary and endothelial organ systems⁴²⁻⁴⁴. Collectively, the findings that nitric oxide protects against

Chinese hamster fibroblast V79 cytotoxicity induced by generation of reactive oxygen species⁴⁵, and the fact that ginseng increases both nitrite and cGMP levels in rat serum and urine⁴⁶, as well as facilitating endogenous nitric oxide release⁴⁷, is strong evidence for an indirect role for ginseng antioxidant activity that involves enhanced nitric oxide synthesis. Further confirmation of this suggestion has recently been reported with the finding that *Panax quinquefolium* inhibited thrombin-induced endothelin release similar to the pharmacological action noted for nitric oxide⁴⁴. Ginseng extracts derived from *Panax ginseng* have also been shown to exhibit a dose-dependent protection against free radical induced injury in pulmonary³⁵ and myocardial⁴⁸ tissue. The fact that crude extracts of ginseng were found to be more effective at inducing this effect, compared with purified ginsenosides (e.g. Rb1 and Rg1), demonstrates a possible synergistic action among different ginseng constituents which occurs only when an extract of ginseng is employed³⁵.

In recent years, numerous components derived from fruit⁴⁹, vegetable⁵⁰, oilseed⁵¹ and herb⁵² plant sources have demonstrated *in vitro* antioxidant activity. *In vitro* studies conducted with *Panax ginseng* have shown a strong tendency to prevent peroxidation of polyunsaturated fatty acids using a transition metal induced lipid oxidation model⁵³. Recent *in vitro* studies using a standardized North American ginseng extract (CNT-2000 from *Panax quinquefolium*) reported direct free radical scavenging of stable radicals as well as the prevention of both site specific and non site specific hydroxyl radical mediated deoxyribose and DNA degradation⁵⁴. This study demonstrated the free radical scavenging activity of North American ginseng using a number of model systems. The question concerning which one, or more, of the specific ginsenoside(s) present in ginseng contributes directly to antioxidant activity, or in concert with other bioactive components, has not been clearly established. Studies

conducted with *Panax vietnamesis* root extract showed inhibition of TBARS formation in mouse tissue homogenate⁵⁵, further supporting antioxidant activity reported by other workers. These workers also showed that ginsenosides Rg1 and Rb1 failed to inhibit hydroxyl radical formation. However, recent studies conducted in our laboratory with Rb1 have led to the conclusion that this ginsenoside inhibits peroxy radical induced DNA breakage (Hu and Kitts, unpublished data). Ginsenosides Rb1, Rb2, Rb3 and Rb, but not Rd, have also been shown to protect against superoxide radical induced damage of cultured cardiac myocytes⁵⁶. Similar *in vitro* studies conducted with individual ginsenosides have indicated some degree of protection against free radical induced endothelial cell damage⁵⁷. Maltol, a principal plant phenolic present in ginseng (e.g. Korean red ginseng) has also been shown to contribute to antioxidant, and little prooxidant activity, as assessed using an iron-catalysed free radical DNA damage model⁵⁸. More research is required to define the source of antioxidant activity characteristic of specific ginseng constituents.

To demonstrate the mechanisms of antioxidant activity of a North American ginseng extract (CNT-2000), a number of *in vitro* model systems were used to characterize ginseng antioxidant activity, thereby suggesting efficacy towards enhancing the stability of different biological macromolecules. Statistical analysis of the experimental data was performed using Student's *t*-test with significant difference set at $P < 0.05$.

Assessing ginseng antioxidant activity *in vitro*

The absorption spectra of 1 mg ml⁻¹ NAGE ginseng (line I) and 100 μM CuCl₂ (line II) in phosphate buffer (pH 7.4) are shown in Fig. 2. Maximum absorbance of 217 nm was common for both the NAGE and CuCl₂ solutions. A shift in absorption maxima from 217 nm to 245 nm occurred in

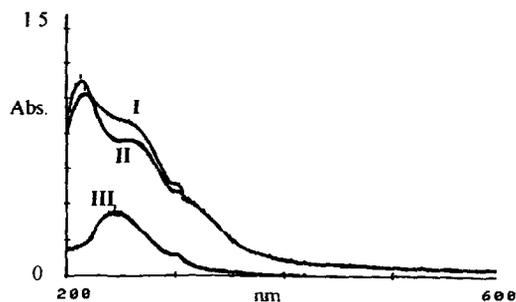


Fig. 2 Copper chelation assay. Briefly, 1 mg ml⁻¹ of NAGE was incubated with 100 μM CuCl₂ at 37°C for 2 h. The spectra of NAGE and CuCl₂-NAGE complex were recorded against 10 mM phosphate buffer (pH 7.4) and corresponding concentration of CuCl₂ in phosphate buffer between 200 and 600 nm. Line 1 = NAGE spectrum; Line 2 = CuCl₂ spectrum; Line 3 = NAGE + CuCl₂ spectrum

the differential spectrum when CuCl₂ was incubated with NAGE (line III), thus denoting chelation of Cu²⁺.

The reducing activity of the NAGE, relative to L-ascorbic acid (Fig. 3 insert), over a wide range of concentrations is shown in Fig. 3. Linear relationships denoting reducing power were obtained for both NAGE ($y = 0.528x + 0.002$, $r^2 = 0.998$) and ascorbic acid ($y = 0.0027x + 0.0014$, $r^2 = 0.999$). Compared with ascorbic acid, NAGE exhibited a limited reducing power. From both standard curves, it was calculated that 1 mg of the NAGE was equivalent to 20.3 ± 0.3 μg ascorbic acid.

The reaction of hydroxyl radical generated from Fenton reactants with DNA is shown in Fig. 4. A concentration-dependent DNA scission reaction was observed with Fe²⁺ (lanes 2–5), indicating a relationship between hydroxyl radical generation and concentration of Fe²⁺ according to the following scheme: $\text{Fe}^{2+} + \text{H}_2\text{O} \rightarrow \cdot\text{OH} + \text{OH}^- + \text{Fe}^{3+}$. The site-specific genotoxic activity of Fenton-induced hydroxyl radicals was characterized by a loss of supercoiled DNA and generation of damaged or nicked circular DNA. The addition of NAGE to the Fenton reactant conditions, with increasing concentrations of Fe²⁺, resulted in complete protection against DNA damage (Fig. 4, lanes 6–10), as reflected by the preservation of the supercoiled DNA and markedly reduced nicked circular DNA.

The ability of NAGE to suppress Cu²⁺-induced human LDL oxidation was assessed by the reduction in the human LDL TBARS, conjugated diene and fluorescence products (Figs 5a and 5b, respectively). The presence of NAGE in this reaction mixture produced a significant ($P < 0.05$) concentration-dependent reduction in Cu²⁺-induced LDL oxidation, as also evaluated by the decrease in electrophoretic mobility on agarose gel (Figs 5c and 5d). The noted inhibition of oxidized LDL on agarose gel corresponded to significant reductions in both TBARS and fluorescence products and, to a lesser extent, changes in conjugated dienes (Fig. 5a). The lower fluorescence readings signified protection of LDL apolipoprotein oxidation from NAGE and were significantly ($P < 0.05$) lower in oxidized LDL but higher ($P < 0.05$) than native LDL, indicating only partial protection against Cu²⁺-induced oxidation. Use of the fluorescence LDL endpoint indicators of peroxidation produced a sensitive assessment of antioxidant activity attributed to NAGE, and corresponded directly with LDL mobility changes that reflected the extent of inhibition of LDL oxidation on the basis of migration on agarose gel (Fig. 5d).

Suppression of DPPH stable radicals by GSH alone and in combination with 0.5 mg ml⁻¹ NAGE is shown in Fig. 6. A NAGE concentration of 0.5 mg ml⁻¹ produced a significant reduction (15%) in DPPH radical activity. GSH alone produced a minimal (8%) reduction in DPPH over a concentration range of 5–100 μM. The combination of NAGE extract with GSH over a wide range of GSH concentrations produced a synergistic scavenging effect

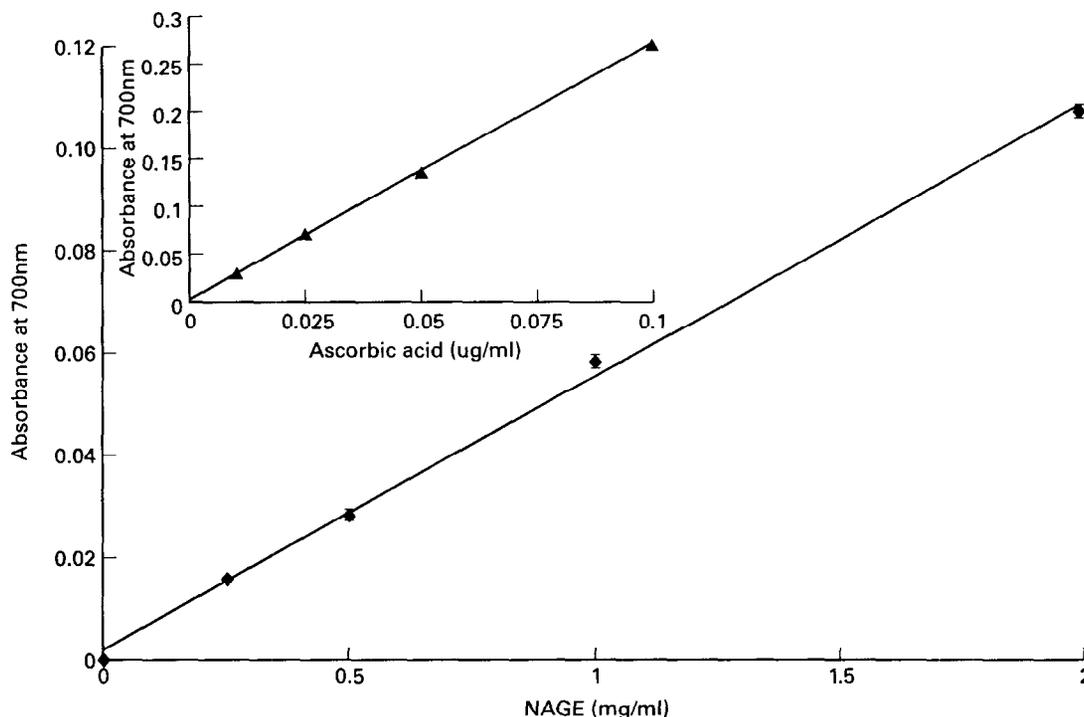


Fig. 3 Reducing power of NAGE: the method followed was that of Hu and Kitts⁵² using L-ascorbic acid for comparison. Briefly, NAGE (0–2.0 mg ml⁻¹ distilled deionized water) was mixed with 2.5 ml of phosphate buffer (0.2 M, pH 6.6) and 2.5 ml of 1.0% potassium ferricyanide and incubated for 20 min at 37°C, followed by the addition of 2.5 ml of 10% TCA solution. A 2.5 ml aliquot of the above solution was mixed with 2.5 ml of distilled deionized water and 0.5 ml of 0.1% ferric chloride, and absorbance measurements were taken at 700 nm. Equivalence of NAGE to ascorbic acid in terms of reducing power was calculated from the working curve of both substances. Insert graph represents reducing activity of ascorbic acid

on quenching DPPH radicals. Maximal ability to quench DPPH radicals was obtained with 0.5 mg ml⁻¹ NAGE and 25–100 µM GSH.

The observation that GSH was effective at scavenging

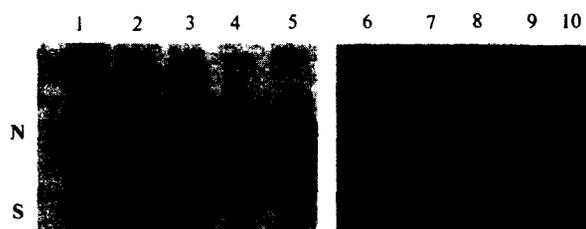


Fig. 4 DNA scission assay: Plasmid (pBR322) DNA from *Escherichia coli* was used to determine the efficacy of a NAGE to modulate metal ion-induced DNA strand scission. Experiments were conducted in phosphate buffer (50 mM, pH 7.4) under ambient oxygen pressure. NAGE (2 µl of 0.005% w/v) was incubated with ferrous sulphate (10, 50, 70 µM) and DNA (0.1 µg ml⁻¹) in a microcentrifuge tube for 60 min at 37°C. The reaction mixture was added to bromophenol blue loading dye (0.25%), containing 0.25% xylene cyanol FF, and 15% ficoll in water and loaded onto an agarose gel for electrophoresis [60 V in Tris acetate–EDTA buffer (0.04 M Tris acetate, 0.001 mM EDTA, pH 7.4)]. Agarose gels were stained with ethidium bromide for 20 min and DNA bands were visualized under UV illumination. Lane 1 = original supercoiled plasmid DNA; Lanes 2–5 = DNA + 5, 10, 50, 70 µM Fe²⁺; Lanes 6–10 = Lanes 2–5 + NAGE (0.005%). S = supercoiled DNA; N = nicked circular DNA

DPPH radicals at a critical concentration confirms an antioxidant activity role to deactivate electrophilic free radicals. GSH is also an important component of the antioxidant enzymes, GSH-P_x and glutathione reductase³², as well as being a critical component in redox cycling for regenerating oxidized ascorbic acid that occurs as a consequence of the regeneration of oxidized α -tocopherol⁵⁹. In the present study, NAGE also effectively scavenged DPPH; however, when in the presence of GSH additional scavenging of DPPH radical was noted. This result denotes a potential degree of synergy between GSH and NAGE. It is noteworthy that GSH has previously been shown to reduce oxidized flavones⁶⁰, which supports our observation that potential important interactions could occur *in vivo* between these non-enzymatic antioxidant constituents in managing whole body oxidative stress. Similar results of potential synergy with GSH and cycoheterophyllin, a prenylflavonoid isolated from leaves of Formosan *Artocarpus heterophyllus*, have also been reported⁶¹.

Safety of ginseng

There are few reported cases of ginseng toxicity or descriptions of side effects attributed to either the quantity or quality of ginseng when taken at the recommended

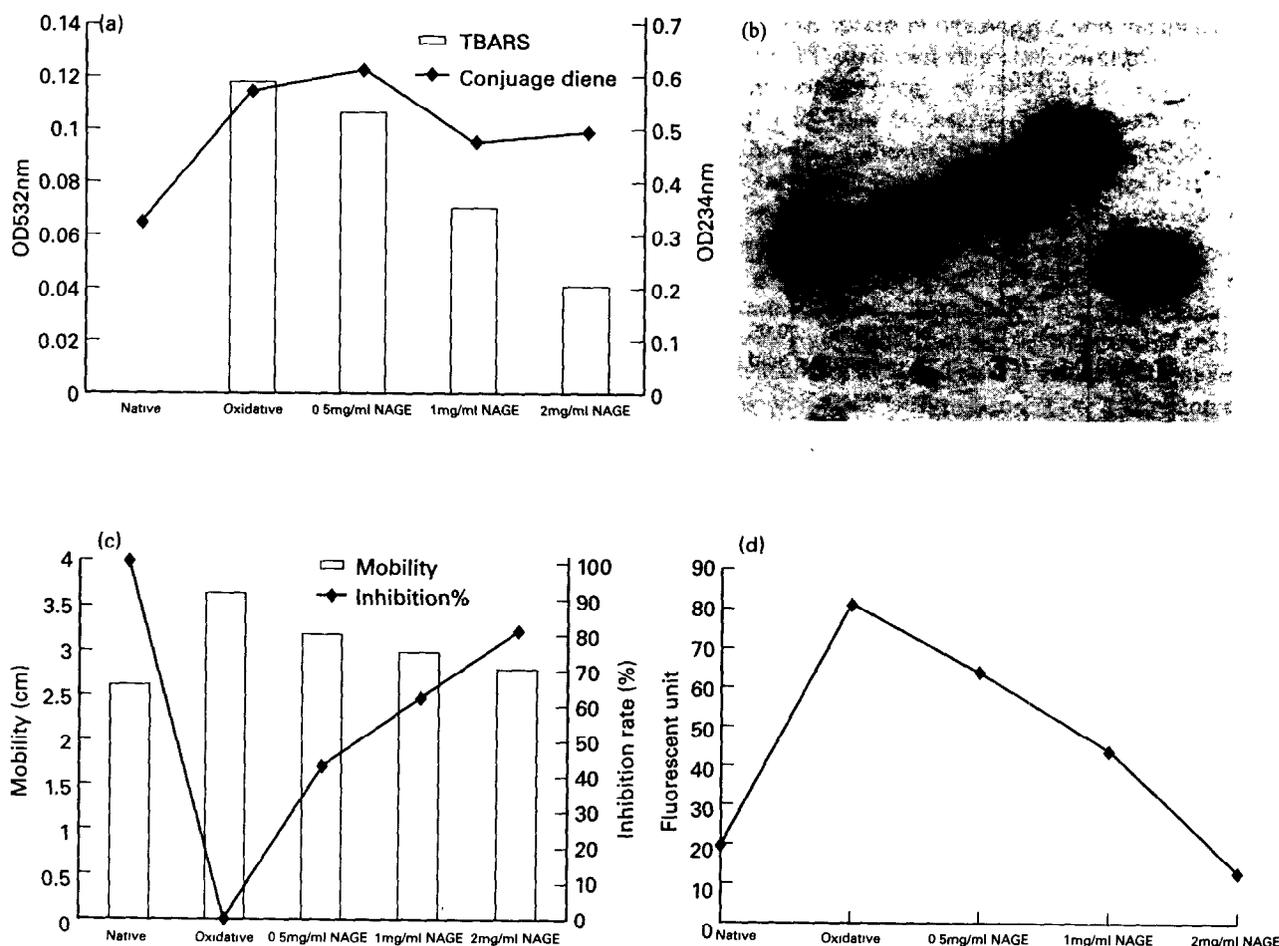


Fig. 5 Copper-mediated human low-density lipoprotein oxidation. Human LDL containing 0.01% EDTA was dialysed against 10 mM phosphate buffered saline (pH 7.4) at 4°C with nitrogen bubbled for 24 h, and the obtained LDL stock solution was stored under N₂ atmosphere in the dark (4°C) for less than 72 h upon expiration⁵². Copper mediated LDL oxidation was performed by incubating LDL (500 µg protein ml⁻¹ in 10 mM phosphate buffer, pH 7.4) with freshly made CuCl₂ (10 µmol l⁻¹) at 37°C for 22 h. Adding 1 mM EDTA stopped the reaction. The extent of LDL oxidation was measured from the following parameters. (a) TBARS was according to the method of Kitts *et al.*⁵⁴ Conjugate dienes were measured at 234 nm with 10 times diluted incubated sample. □ = TBARS; ◆◆◆ = conjugate diene. (b) LDL oxidation was evaluated with agarose gel (0.6%) electrophoresis running in 50 mM barbital buffer, pH 8.6 and staining with Sudan Black B. (c) Mobility of native and oxidized LDL. Percentage inhibition on agarose gel electrophoresis was calculated as follows: Inhibition rate (%) = (C - S)/C × 100%, where C = electrophoretic mobile distance (cm) of LDL treated with CuCl₂ and S = electrophoretic mobile distance (cm) of LDL treated with CuCl₂ as well as CNT-2000. □ = mobility, ◆◆◆ = % control mobility inhibition. (d) Fluorescence readings of native and oxidized LDL were taken with 30 times diluted sample in PBS (pH 7.4) at emission (430 nm) and excitation (360 nm) wavelengths

dosages. A careful evaluation of many of these reports has been published by Vogler *et al.*⁴ Early animal studies, conducted in dogs, reported no adverse effect of ginseng on body weight or blood chemistry⁶². In mice, the LD₅₀ for ginseng ranges from 10 to 30 g kg⁻¹ (Ref. 17), with a lethal oral dose of purified ginseng as high as 5 g kg⁻¹ body weight⁶². In a 2 year human study, 14 out of a total of 133 subjects were reported to experience side effects attributed to long-term exposure of ginseng when consumed at levels up to 15 g day⁻¹ (Ref. 63). Average intakes of ginseng were equivalent to consuming 6 × 500 mg ginseng capsules daily and produced side effects that included hypertension, gastrointestinal disturbances, insomnia and nervousness. The validity of these observations is difficult to evaluate because of the absence of a

placebo treatment in the study and the fact that subjects were not controlled for other bioactive substance intake (e.g. caffeine). Moreover, as is the case with many studies with ginseng, the ginsenoside content of the ginseng consumed was not determined. Notwithstanding this, however, other subjects from this study who had consumed extremely high intakes of ginseng (e.g. greater than 15 g day⁻¹), showed symptoms of confusion and depression. This level of ginseng consumption far exceeds the German Commission E's⁶⁴ recommended daily intake of 1–2 g day⁻¹ of Asian ginseng, containing 4–5% ginsenoside⁶⁵.

Ginseng may contain an endocrine-like active substance which can affect neonate development⁶⁶. In one study, oestrogen-like activity attributed to chronic ginseng

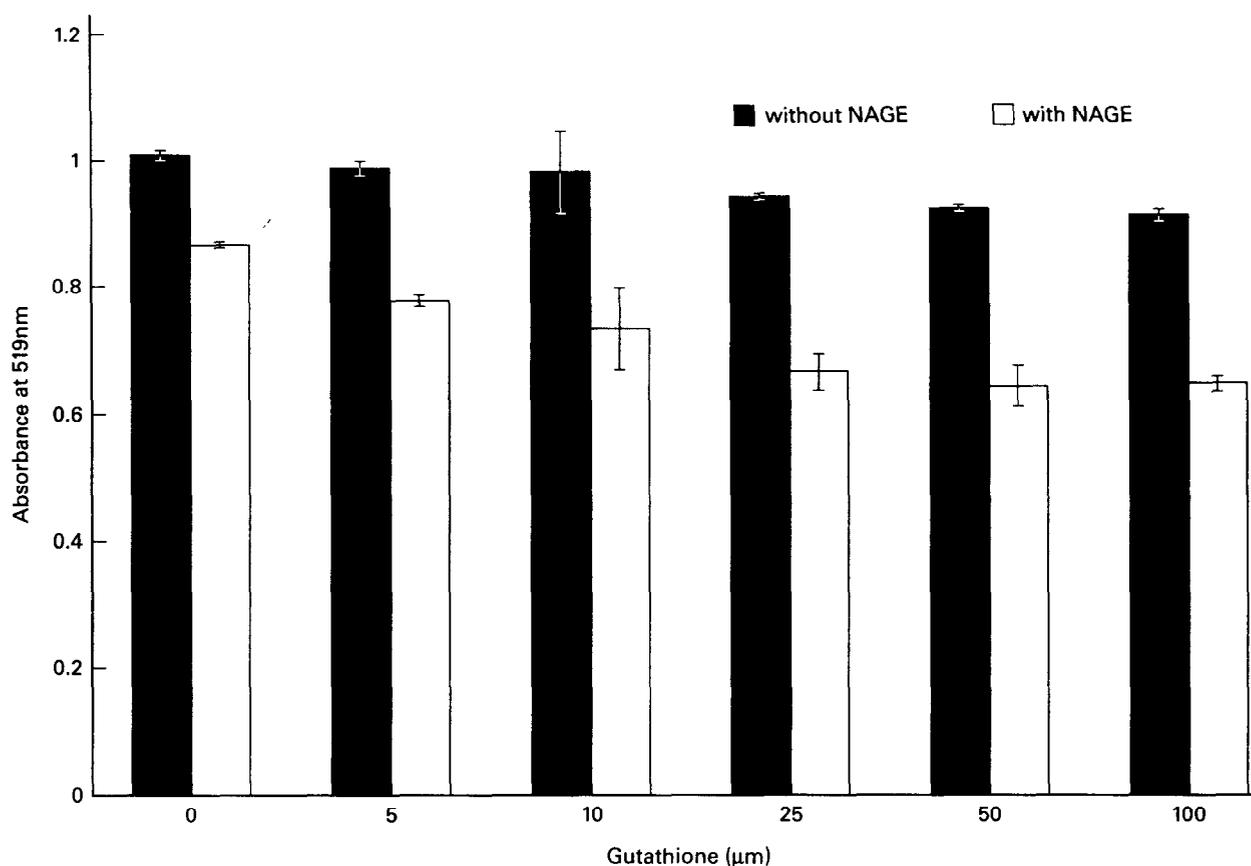


Fig. 6 Regeneration of CNT-2000 by glutathione in 1,1-diphenyl-2-picrylhydrazyl analysis. A solution of DPPH stable radical (0.1 mM) was made to a final concentration in ethanol (95%) and was incubated with CNT-2000 (0.5 mg ml⁻¹), as well as with various amounts of glutathione. Absorbance readings were taken at 519 nm using a spectrophotometer. ■ = without NAGE; □ = with NAGE

use was reported to cause swollen and painful breasts⁶⁷. Ginseng–drug interactions have been observed in a few isolated situations, which include phenelzine, a monoamine oxidase inhibitor⁶⁸, and warfarin⁶⁹, an agent used to modulate blood viscosity factors. In both reports, there was little information that adequately characterized the prevalence and extent of risk attributed to this interaction. It is noteworthy, however, that caution has been expressed concerning the use of Asian ginseng to combat acute stress, due to the fact that the hypertensive effect associated with these individuals is contra-indicated⁷⁰.

Finally, with the antioxidant characterization of ginseng reported herein, no prooxidant activity of the NAGE was observed. The copper chelating activity and low reducing potential of the NAGE represented an interesting property not present for all bioactive plant compounds possessing antioxidant activity. Compounds such as ascorbic acid^{71–73} as well as polyphenolics, including myricetin^{74,75} and the catechins in green tea⁷⁵, are effective metal chelators and thus possess antioxidant activity. Owing to their substantial reducing power, these compounds can also behave as prooxidant agents to carbohydrates, protein

and DNA by reducing metal ions in redox reactions that are intrinsically involved in enhancing the rate of hydroxyl radical generation by the Haber–Weiss reaction⁷⁶, resulting in eventual breakdown of these macromolecules. The high redox potential of ascorbic acid has been shown to accelerate reduction of Cu²⁺ to its lower valency Cu¹⁺ in aqueous medium and to promote accelerated DNA strand scission⁷⁷. Our characterization of the NAGE in this study suggests that the formation of a Cu²⁺–ginseng complex was sufficient to inhibit a further reaction with H₂O₂ and subsequent generation of a hydroxyl radical induced prooxidant activity. Further confirmation of this suggestion was obtained with the site-specific 2-deoxyribose assay results shown in Fig. 7. Owing to the limited reducing power of NAGE, very little prooxidant activity was observed over the concentration range 0.25–2 mg ml⁻¹ NAGE in the presence of a Cu²⁺-mediated Fenton reaction. The formation of TBARS, derived from 2-deoxyribose fragment production and resulting in hydroxyl radical generated from the Fenton reaction was greatest with L-ascorbic acid and only minimally increased with higher North American ginseng concentrations.

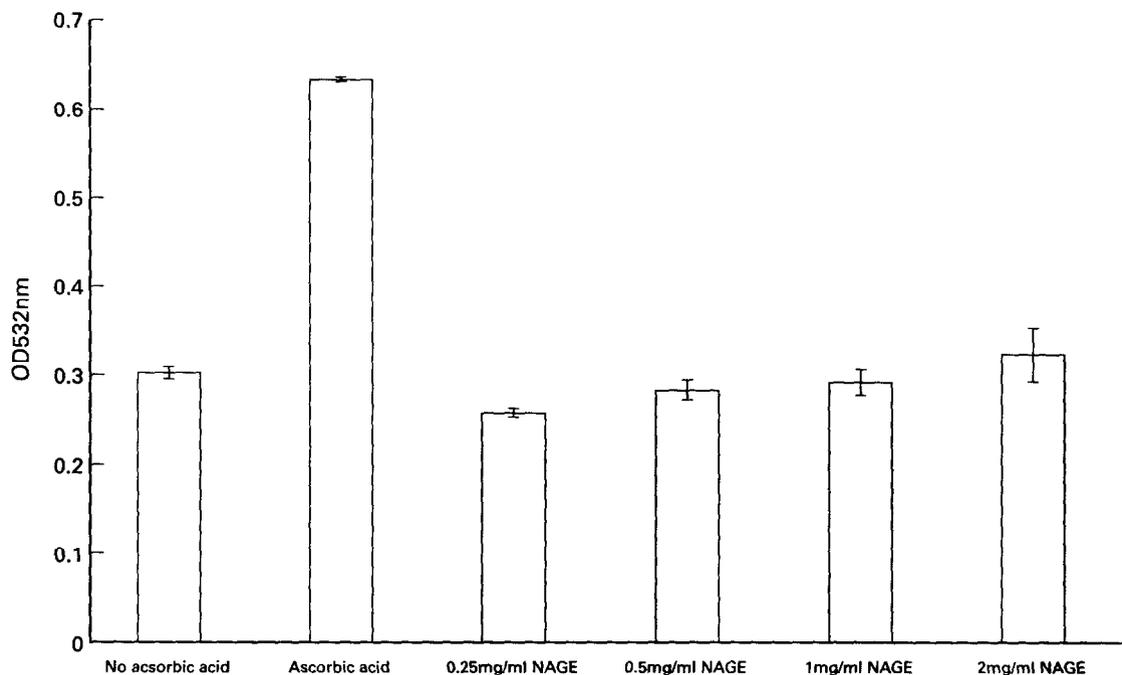


Fig. 7 Prooxidant assay. A modification of the method reported by Kitts *et al.*⁵⁴ was used. Briefly, the reaction system contained 3.6 mM 2-deoxyribose, 0.1 mM CuCl₂, 1 mM H₂O₂, 0.1 mM EDTA as well as the sample. The reaction mixture was incubated at 37°C for 1 h, followed by mixing with an equal volume of 10% (w/v) TCA and 0.5% TBA. OD_{532nm} measurements were taken after samples were incubated at 100°C for 15 min. If absorbance readings taken at 532 nm were higher than that of treatment without ascorbic acid, prooxidation was confirmed. Values represent mean ± SEM ($n = 8$)

Conclusions

Ginseng has been shown in many studies to possess biological activity, but only recently have the specific mechanisms underlying these biological activities been shown at both the molecular and cellular levels. An inherent difficulty in many studies was the use of undefined ginseng extracts, which precluded confirmation of findings and absolute assessment of efficacy and safety by subsequent studies whereby different sources of ginseng were employed. This limitation is particularly true for ginseng, as evidenced by the apparent differences in pharmacological effects noted between *Panax ginseng* and *Panax quinquefolium*, and the fact that these prominent species of ginseng vary characteristically from the standpoint of the complex mixture of numerous potentially bioactive constituents (e.g. ginsenosides). The implications that this has for commercial products were pointed out in a survey of 50 commercial ginseng preparations, from 11 different countries, in which greater than 90% of the preparations varied between 2 and 9% in total ginsenoside content and some preparations contained no ginsenosides⁷⁸. The availability of standardized extracts for both Asian and North American ginseng will assist greatly in advancing our knowledge on the role of this traditionally used herb as a dietary modulator of various physiological processes. The availability of standardized extracts of both Asian and North American

ginseng will also complement the additional need for comparative, controlled double-blind human clinical studies that will assess the relative efficacy and safety of ginseng.

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CLINICAL TRIALS

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The efficacy of ginseng. A systematic review of randomised clinical trials

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Abstract Objective: Ginseng is one of the most popular herbal remedies, and a number of health claims are made for it. This systematic review provides an evaluation of the current evidence for or against the efficacy of ginseng root extract.

Methods: Searches of the computerised literature databases Medline, Embase, Biosis, CISCOM and the Cochrane Library were performed to retrieve double-blind, randomised, placebo-controlled trials of ginseng root extract for any indication. Manufacturers and experts were contacted to provide additional information. There were no restrictions regarding the language of publication. The outcome and methodological quality of all trials were independently assessed by two reviewers.

Results: Sixteen trials met the inclusion criteria and were reviewed. These trials related to physical performance, psychomotor performance and cognitive function, immunomodulation, diabetes mellitus and herpes simplex type-II infections. The evidence found for ginseng root extract is compelling for none of these indications.

Conclusion: Based on these data, it is concluded that the efficacy of ginseng root extract is not established beyond reasonable doubt for any of these indications. The widespread use of ginseng as a herbal remedy warrants more rigorous investigations to assess its efficacy and safety.

Key words Ginseng · Herbal medicine · Alternative medicine

Introduction

Complementary/alternative therapies (CATs) are increasingly used by the general population. In the US, for

instance, it has been suggested that 40% of the public use such therapies [1]. Herbal medicine is among the most prevalent CATs [1, 2, 3]. This is also confirmed by a recent assessment of the US herbal market [3]. In 1998, total US sales for herbal remedies approached US \$4 billion, suggesting an annual growth rate of approximately 25% [4]. The annual turnover of ginseng was US \$98 million with a growth rate of 26% [3].

Ginseng root extracts have long been used in traditional Chinese medicine to restore and enhance well-being. These adaptogenic effects are described as increasing the resistance against noxious or stressful influences without impairing physiological functions [5]. Ginseng comprises a number of different species, which belong to the same plant family, the *Araliaceae*. Korean, Japanese and American ginseng belong to the genus *Panax*, while Siberian ginseng is of the genus *Eleutherococcus* (Table 1). More detailed information and botanical descriptions can be found elsewhere [6].

Ginseng is included in the Pharmacopoeias of several countries, such as China, Germany and the UK [7]. It is widely available as an over-the-counter food supplement. Modern therapeutic claims refer to vitality, immune function, cancer, cardiovascular diseases and sexual function [8, 9]. These claims are mostly based on uncontrolled or non-randomised studies [10]. Uncontrolled studies cannot differentiate between non-specific effects, such as the natural course of disease, and specific therapeutic effects [11]. Non-randomisation may lead to a substantial overestimation of the effect size [12]. Therefore, randomised controlled trials (RCTs) are needed to determine the true efficacy of ginseng. The aim of this study was to assess the current evidence from RCTs for or against the efficacy of ginseng.

Methods

Systematic literature searches were performed to identify all RCTs on ginseng. Computer databases were Medline, Embase, Biosis, CISCOM (Research Council for Complementary Medicine,

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Table 1 Medicinally used ginseng species

| Common name | Botanical name |
|---|--|
| *Korean or Chinese or Asian ginseng | <i>Panax ginseng</i> C.A. Meyer |
| Japanese ginseng | <i>Panax japonicus</i> C.A. Meyer |
| *American ginseng | <i>Panax quinquefolium</i> L. |
| San-chi or Tien-chan ginseng | <i>Panax notoginseng</i> (Burk.) |
| Vietnamese ginseng | <i>Panax vietnamensis</i> (Ha et Grushv) |
| *Siberian or Russian or Eleuthero ginseng | <i>Eleutherococcus senticosus</i> (Maxim.) |

* Most commonly used

London, UK) and the Cochrane Library (all from their respective inception to September 1998). The search terms used were ginseng, panax and eleutherococcus. A manual search was performed using the bibliographies of studies and reviews located through the search in the computer databases and through scanning our own files. Manufacturers of commercial ginseng products were asked to contribute further information. In addition, leading experts of herbal medicine were contacted to provide published and unpublished material [13].

RCTs of ginseng root extract (*Panax* species and *Eleutherococcus senticosus*) were included if performed double-blind and related to the administration of ginseng mono-preparations. Trials for any indication were included. Studies of ginseng in combination with other substances were excluded. No restrictions regarding the language of publication were imposed. Data were extracted in a standardised, predefined manner independently by two authors (BKV, MHP). Methodological quality was assessed using the system developed by Jadad (with items on random allocation, double-blinding and description of dropouts and withdrawals) [14]. Other criteria for data extraction are shown in Table 2. The authors met to agree consensus on the assessed data. Discrepancies were settled through discussions.

Results

A total of 57 RCTs on ginseng were retrieved [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71]. Forty-one trials were excluded, 8 because they were not reported as double blind [31, 32, 33, 34, 35, 36, 37, 38], 30 were conducted on ginseng in combination with other substances [39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68] and 3 trials were not performed using ginseng root extract [69, 70, 71]. Sixteen studies met the aforementioned criteria and were included [15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. These trials assessed the effects of ginseng root extracts on physical performance, psychomotor performance and cognitive function and immunomodulation. Key data are summarised in Table 2, while the main results are described below.

Physical performance

Seven trials investigated the effects of ginseng root extract on physical performance in young, active

volunteers during submaximal and maximal exercise cycle ergometers [15, 16, 17, 18, 19, 20, 21]. The most recent studies found no improvement of physical performance after ingestion of *Panax ginseng* [20], *Panax quinquefolium* [18] or *Eleutherococcus senticosus* [19]. Other studies found a significant decrease in heart rate and an increase in maximal oxygen uptake compared with placebo [15, 16, 17], which persisted 3 weeks after the treatment [16].

Psychomotor performance and cognitive function

Five studies investigated the effects of ginseng on psychological functions. Four of these were conducted in young, healthy volunteers [22, 23, 24, 25], while the non-placebo-controlled trial was performed on elderly people [26]. Three studies [23, 24, 25] report significant improvements ($P < 0.05$) in mental arithmetic and abstraction tests with *Panax ginseng* and in self-memory tests with *Eleutherococcus*. In the latter study, ginseng was administered in the control group and reported to be inferior compared with a combination of neurotrophic aminoacids and vitamin B₁₂. The attention test and inverted counting test, however, significantly ($P < 0.05$) improved compared with baseline in the group treated with ginseng [26].

Four studies [18, 19, 21, 22] investigated whether ginseng may alter psychological functions and improve tolerability to exercise-induced stress. This hypothesis was confirmed by none of these studies. They suggest no significant effects on the ratings of perceived exertion during cycle ergometer tests.

Immunomodulation

Two studies assessed the effects of ginseng on the immune system in healthy volunteers [27, 28]. One study [27] reports a significant ($P < 0.05$) increase of the number of T lymphocytes and of the activity of T lymphocytes compared with baseline after the ingestion of standardised *Panax ginseng*. A more recent study, however, found no effects on total and differential white blood cell counts and lymphocyte subpopulations.

Miscellaneous

Sotaniemi and co-workers [29] assessed patients newly diagnosed type-II diabetes mellitus, who received either 100 mg or 200 mg ginseng daily. At the end of an 8-week treatment period, psychophysical performance, mood and vigour were significantly ($P < 0.05$) improved compared with baseline in both ginseng groups. HbA_{1c} was significantly reduced ($P < 0.05$) in patients who received 200 mg ginseng, while a reduction of the fasting blood glucose level was observed in both ginseng groups compared with baseline.

Table 2 Double-blind, randomised controlled trials of ginseng root extract. *Elagen* standardised extract from *Eleutherococcus senticosus* (Eleutherosides B, E); *G115* standardised ginseng extract (containing 100 mg of a 4% ginsenoside concentration from Korean *Panax ginseng*); *G115S* standardised ginseng extract (containing 100 mg of a 7% ginsenoside concentration from Korean *Panax ginseng*); *ESML Eleutherococcus senticosus* Maxim L extract (including eleutherosides B, E and ethanol 30–34%)

| First author [reference] | Jadad score (maximum: 5) | Design | Patients entered and sample size (ginseng/control) (age in years) | Intervention/control (dosage) | Primary endpoint | Main results | Frequency of adverse effects (ginseng/control) |
|-----------------------------|--------------------------|---------------------------------------|---|---|--|---|--|
| Physical performance | | | | | | | |
| Forgo [15] | 3 | Placebo-controlled; 3 parallel groups | 30 Healthy sportsmen 10/10/10 (range 18–31) | G115 S (100 mg twice daily)/G115 + Vitamin E (100 mg, 200 mg respectively twice daily)/placebo for 9 weeks | Change of aerobic capacity, serum lactate, heart rate, hormone levels during ergometer exercise | Oxygen absorption significantly increased ($P < 0.01$), serum lactate and heart rate significantly decreased ($P < 0.05$) in both ginseng groups compared with placebo, no change of LH, testosterone and cortisol levels | Not reported |
| Forgo [16] | 3 | Placebo-controlled; 2 parallel groups | 28 Healthy athletes 14/14 (range 20–30) | G115 (100 mg twice daily)/placebo for 9 weeks | Oxygen uptake and heart rate during ergometer exercise, duration of effect | Oxygen uptake significantly increased ($P < 0.05$) and heart rate significantly decreased ($P < 0.01$) compared with placebo; effects persisted at a 3-week follow-up assessment | Not reported |
| Cherdrungsi [17] | 4 | Placebo-controlled; 4 parallel groups | 41 Healthy students 10/10/10/11 (range 19–26) | Standardised <i>Panax ginseng</i> extract (150 mg twice daily)/ + exercise or placebo/ + exercise for 8 weeks | Maximal oxygen uptake during cycle ergometer exercise, leg muscle strength, body fat, resting heart rate | Body fat significantly decreased in both ginseng groups compared with baseline ($P < 0.05$); subjects in the ginseng group without exercise improved maximal oxygen uptake, resting heart rate and leg strength compared with the placebo group without exercise ($P < 0.05$) | None |
| Morris [18] | 2 | Placebo-controlled; cross-over | 8 Sportive volunteers 8/8 (mean 27) | Purified ethanolic <i>Panax quinquefolium</i> extract (618 mg or 1235 mg once daily)/placebo for 1 week | Oxygen uptake, heart rate, time to exhaustion, mean lactate concentration, rating of perceived exertion during submaximal ergometer exercise | No significant intergroup differences in any of these outcome measures | Not reported |

Table 2 (continued)

| First author [reference] | Jadad score (maximum: 5) | Design | Patients entered and sample size (ginseng/control) (age in years) | Intervention/control (dosage) | Primary endpoint | Main results | Frequency of adverse effects (ginseng/control) |
|--|--------------------------|---|---|--|---|--|---|
| Dowling [19] | 3 | Placebo-controlled; 2 parallel groups | 20 Trained distance runners 8/8 (mean 37) | ESML (3.4 ml once daily)/placebo for 6 weeks | Oxygen uptake, respiratory exchange ratio, heart rate, lactate level and rating of perceived exertion during maximal ergometer exercise | No significant intergroup differences in any of these outcome measures | Not reported |
| Engels [20] | 3 | Placebo-controlled; 2 parallel groups | 19 Healthy women 10/9 (range 21–35) | G115 (100 mg twice daily)/placebo for 8 weeks | Maximal work performance, oxygen uptake, respiratory exchange rate, blood lactate, heart rate during graded cycle ergometry test to exhaustion | No significant intergroup differences in any of the measured parameters | None |
| Engels [21] | 4 | Placebo-controlled; 3 parallel groups | 36 Healthy men 10/11/10 (mean: 23/26/27) | G115 (400 mg daily)/G115 (200 mg daily)/placebo for 8 weeks | Oxygen consumption, respiratory exchange rate, heart rate, lactate concentration, rating of perceived exertion during graded ergometer exercise to exhaustion | No significant difference between ginseng and placebo groups in any of the measured parameters | Three cases of diarrhoea in high dose ginseng group |
| Psychomotor performance and cognitive function | | | | | | | |
| Smith [22] | 2 (abstract) | Placebo-controlled; 2 parallel groups | 19 Healthy women 10/9 (mean: 26) | G115 (200 mg daily)/placebo for 8 weeks | Profile of mood states, rating of perceived exertion after submaximal and maximal ergometer exercise | No significant intergroup differences in these parameters | Not reported |
| D'Angelo [23] | 4 | Placebo-controlled; 2 parallel groups | 32 Male volunteers 16/16 (range 20–24) | G115 (100 mg twice daily)/placebo for 12 weeks | Cancellation test, digit symbol substitution test, mental arithmetic test, choice reaction time | Significant intergroup differences ($P < 0.05$) in favour of ginseng in mental arithmetic test | None |
| Sørensen [24] | 4 | Placebo-controlled; 2 parallel groups | 127 Healthy volunteers 55/57 (range: 40–70) | Standardised <i>Panax ginseng</i> extract (400 mg daily)/placebo for 8–9 weeks | Psychomotor tests, concentration, learning and memory, abstract thinking tests | Significantly better abstraction test in ginseng group compared with placebo ($P < 0.02$) | None |
| Winther [25] | 2 (abstract) | Placebo-controlled crossover; 4-armed study | 24 Healthy volunteers sample size not reported (range: 36–58) | <i>Eleutherococcus senticosus</i> (625 mg twice daily)/ <i>Ginkgo biloba</i> (28.2 mg flavonglycoside and 7.2 mg terpenlactone daily)/vitamins/ placebo for 3 months | Concentration test, selective memory test | Selective memory significantly improved compared with placebo ($P < 0.02$) | Not reported |

| [reference] | Quality score (maximum: 5) | Design | Patients entered and sample size (ginseng/control) (age in years) | Intervention/control (dosage) | Primary endpoint | Main results | Frequency of adverse effects (ginseng/control) |
|------------------------------------|----------------------------|---|--|--|---|---|---|
| Garcia [26] | 2 | Comparative trial; 2 parallel groups | 50 Elderly patients 26/24 (range: 65-80) | Neurotrophic amino-acids + vitamin B ₁₂ (dose not reported)/ <i>Panax ginseng</i> extract (dose not reported) for 4 weeks | Association test, digit symbol test, inverted counting test | Ginseng was inferior compared with control in each of these parameters, association test and inverted counting test significantly improved ($P < 0.05$) compared with baseline | Not reported |
| Immunomodulation Scaglione [27] | 4 | Placebo-controlled; 3 parallel groups | 60 Healthy volunteers 20/20/20 (range: 18-50) | G115 (100 mg twice daily)/aqueous ginseng extract (100 mg twice daily)/ placebo for 8 weeks | Chemotaxis of polymorphonuclear leucocytes, percentage of total T-lymphocytes, | Significant increase ($P < 0.05$) of both parameters in both ginseng groups after 4 weeks and 8 weeks of treatment compared with baseline | Not reported |
| Srisurapanon [28] | 3 | Placebo-controlled; 2 parallel groups | 20 Healthy males 10/10 (range: 21-22) | Standardised ginseng extract (300 mg once daily)/placebo for 8 weeks | Total and differential leucocyte count, lymphocyte subpopulations CD3, CD4 CD8, CD4/8 ratio, CD19, CD25 | No significant intergroup differences in any of these parameters | Not reported |
| Miscellaneous Sotaniemi [29] | 3 | Placebo-controlled; 3 parallel groups multicentre | 36 Patients with type-II diabetes mellitus 12/12/12 (mean: 59/57/60) | Ginseng (100 mg once daily)/ginseng (200 mg once daily)/ placebo for 8 weeks | Mood, vigour, psychophysical activity, fasting blood glucose levels | Significant ($P < 0.05$) improvement of mood, vigour, psychophysical activity and fasting blood glucose levels in both ginseng groups compared with baseline, significant ($P < 0.05$) improvement of HbA _{1c} compared with baseline (ginseng 200 mg) | None |
| Williams [30] | 4 | Placebo-controlled; 2 parallel groups | 93 Volunteers of the Herpes Association 44/41 (not reported) | Elagen (400 mg once daily)/placebo for 6 months | Frequency, severity, duration of herpes episodes | 75% of patients in the treatment group reported improvement in frequency, severity and duration compared with 34% in the placebo group | Tiredness (1/0); acid stomach (1/0); runny nose (0/2); headache (0/2) |

Williams et al. [30] administered 400 mg of standardised *Eleutherococcus* extract once daily for 6 months. A significant ($P=0.0002$) beneficial effect on frequency, severity and duration of herpes simplex type-II infections is reported in the ginseng group compared with placebo.

Discussion

This study reviewed 16 double-blind RCTs of the most frequently used ginseng species. Trials of ginseng for any indication were included to assess the range of health claims made for this plant extract. The efficacy was evaluated assessing double-blind RCTs of ginseng root mono-preparations.

The perhaps most striking finding is the relative paucity of evidence for any particular condition. Less than half of the studies were of good methodological quality, scoring more than three points on the system developed by Jadad (Table 2). Small sample sizes, varying dosages and unclassified preparations of ginseng are further limitations.

It is noteworthy that a number of studies were supported by manufacturers of ginseng products, which may have introduced a degree of bias. Most trials sponsored by the industry revealed a positive outcome. Although this type of bias is of concern for systematic reviews, regarding the conclusion of the present study this concern does not apply. In an attempt to minimise bias, no restrictions regarding the language of publication were imposed. The search strategy included four databases with a focus on the mainstream medical literature as well as one database specialising in complementary medicine. In addition, experts on the subject were contacted to retrieve particularly unpublished articles. Despite the extensive literature search and the fact that the authors were able to locate and translate studies in Dutch, Swedish and Spanish as well as trials in Russian, Korean and Chinese, trials may have been missed and there is no guarantee that all trials were identified.

Although *Eleutherococcus* ginseng and *Panax ginseng* are used for similar indications, their respective active constituents are different. Ginsenosides are the active constituents of *Panax ginseng*. Twenty-eight different subtypes have been described so far [72], and the concentrations of the individual ginsenosides vary related to the source (wild or cultivated), the plant part, the part of the root, year of growth as well as between species and commercial brands [73, 74, 75, 76, 77, 78]. For *Eleutherococcus senticosus*, however, a heterogeneous group of mostly glycosides is thought to be the main active constituents [79].

Ginseng and its constituents have been reported to stimulate the immune system in animals and in human cells [80, 81, 82, 83]. Ginseng may exhibit anti-carcinogenic activity [84, 85, 86], improve learning and memory [87, 88, 89] and increase resistance to radiation, viral and

tumorload, temperature, stress and physical exercise animal experiments [90, 91]. An interaction of ginseng with nitric oxide has also been suggested and may contribute to possible cardiovascular and aphrodisiac properties [92, 93].

Adverse effects (AEs) of ginseng were reported only two of the reviewed RCTs (Table 2). For *Panax ginseng*, three cases of diarrhoea were reported [72] while one case each of tiredness and acid stomach were reported with *Eleutherococcus senticosus* [30]. Several anecdotal reports of AEs and drug interactions are described in the literature. One case of explosive headache, nausea, vomiting, chest tightness and cerebral arteritis was reported as an acute toxic reaction to a dose of approximately 25 g *Panax ginseng* [94]. Other AEs relate to the oestrogen-like activity of ginseng. Cases of vaginal bleeding are described after the use of Rumanian and Chinese ginseng, one of them after topical use [95, 96, 97]. Six cases of mastalgia were related to ginseng intake [98, 99]. Swollen, tender breasts and increased libido were reported. Other case reports refer to overactive behaviour in a schizophrenic patient on ginseng as a possible cause for Stevens-Johnson syndrome and a manic episode in a depressed patient [100, 101, 102].

A "ginseng-abuse syndrome" has been described in 14 of 133 long-term ginseng users [103]. The average daily dose was 3 g of *Panax ginseng* root material. The patients experienced hypertension, nervousness, sleeplessness, skin eruptions and morning diarrhoea; some subjects also became euphoric and agitated. Doses of 15 g were associated with depersonalisation and confusion, while depression was reported after more than 1 g of *Panax ginseng* per day [103]. Furthermore, herb-drug interactions have been reported. Ginseng may inhibit the effects of warfarin [104] and interact with monoamine oxidase inhibitor phenelzine [105]. Of such case reports fail to provide sufficient details on, for instance, the type or quality of ginseng used, or indeed whether the preparation actually contained ginseng [106, 107].

In conclusion, there is contradictory evidence for ginseng to improve physical performance and immunological parameters. Ginseng may have beneficial effects on psychomotor performance and cognitive behaviour. No trial confirmed the alleged age-delaying properties of ginseng. The results suggesting a reduction of blood glucose levels in type-II diabetic patients need further investigation. Thus, according to these data, there is no compelling evidence for none of the claimed indications. The widespread use of ginseng as a herbal remedy warrants more rigorous investigations to assess its efficacy and safety.

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Attachment 9:

Acute oral toxicity test of Sustotrong



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| Test Report | No. 2000099/BC | Date Dec 25 2000 |
|--------------------|----------------|------------------|

Introduction and Purpose

The purpose of this safety test is to determine if acute health hazards are associated with ingestion of the test article. The measure of acute toxicity can be expressed as the median lethal dose (LD50), a statistically derived value that estimates the dose that would theoretically kill 50% of the test animal group. Such tests require the dosing of a relatively large number of animals to generate precise LD50 values.

Often such a precise measurement of lethality is either not required to characterise the test article or may not be practical as the test article may be minimally toxic to animals following oral administration. To minimise the number of animals used in acute oral toxicity tests without compromising the intent of such safety tests, the use of limited screening tests with the administration of a single, high limit dose to a group of animals is often adequate for assessing the inherent acute toxicity of the test article.

The test was conducted in accordance with the procedures as outlined in :

Procedures for Toxicological Assessment on Food Safety
Acute Toxicity Test
GB15193.3-94

The study was monitored by SGS Hong Kong Ltd Bio-Sciences Division, Room 301-4, Hong Kong Institute of Biotechnology, 2 Biotechnology Avenue, 12 Miles, Tai Po Road, Shatin, Hong Kong and performed by Ministry of Health (MOH) approved site during October 19 November 2, 2000.

Summary

When tested as specified herein, the test article identified by the client as 喜多壯冬蟲夏草 did not induce any mortality in laboratory animals following a single dose administration at 20g/kg and was considered to have an acute oral LD50 value greater than 20g/kg.

While the term non-toxic is not defined by any scientific body or regulatory agency, in general, Toxicological Assessment on Food Safety issued by Ministry of Health (MOH) Peoples Republic of China (PRC) recognise substances as being acutely "toxic" if the test article induces mortality in animals administered doses at up to 5.0g/kg.

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| | | |
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| Test Report | No. 2000099/BC | Date Dec 25 2000 |
|--------------------|----------------|------------------|

Test Animals

Strain : NIH mice (male, female)
 Source : Guangdong Provincial Medical Laboratory Animals Supply Centre
 (廣東省醫學實驗動物中心)
 Date(s) Received : 14/10/2000

Upon arrival, animals were housed in the observation battery rack and hair dyed on different part of the body for animal identification. Animals were observed for at least 5 days for signs of illness or disease prior to initiating tests.

Sample Preparation

A test solution was prepared by dissolving the test sample with distilled water to a concentration of 500mg/ml. A single dose administration of 0.4ml/10g body weight using needle and syringe was given. The control group were treated with same amount of distilled water.

Test Article

Sample Description : 喜多壯冬蟲夏草
 Quantity : 550g
 Manufacturer/Supplier : Sheng Chang Pharmaceutical Co., Ltd.
 Country of Origin : Taiwan
 Country of Destination : Hong Kong (South East Asia)
 SGS Sample No. : 1070573-102
 Sample Receiving Date : 14/10/2000
 Sample Receiving Condition : Capsules in sealed aluminum containers

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B110/b4

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|--------------------|----------------|------------------|
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Results

Definitive Testing, Acute Oral Toxicity Upper Limit Test

40 NIH mice (20 male, 20 female) were administered an oral dose of the test article 20g/kg.

Testing Period : 19/10/2000 - 02/11/2000

| Group | No. of Animals | Dose (g/kg) | 14-day Mortality % Total | Average Body Weight (g) | | P Value |
|---------------|----------------|-------------|--------------------------|-------------------------|-------|---------|
| | | | | Initial | Final | |
| Test Group | M 10 | 20 | 0 | 20.49 | 29.98 | >0.05 |
| | F 10 | 20 | 0 | 20.64 | 27.01 | >0.05 |
| Control Group | M 10 | -- | 0 | 20.92 | 30.83 | |
| | F 10 | -- | 0 | 21.55 | 26.51 | |

Observations

All animals appeared normal throughout the 14-days observation period. There were no differences of body weights between test group and control group (P >0.05).

Conclusion

When tested as specified, the test article identified by the client as ^(Sustotrong) 喜多壯冬蟲夏草 was considered to be essentially non-toxic to laboratory animals following oral administration at 20g/kg.

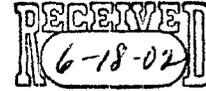
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B10765



MARCO POLO TECHNOLOGIES, INC.

A Green Pharmaceutical Company



TO: Dr. Felicia B. Satchell, Director
Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling,
and Dietary Supplement (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Notification tracking #79967

DATE: June 18, 2002

Dear Dr. Satchell:

This letter is in reference to our original notification dated March 31, 2002 on a dietary supplement "Sustotrong" (distributed by HOME GI BIOTECH INTERNATIONAL CORP.) and my conversation with Ms Rhonda Kane dated June 7, 10 and 12, 2002. The following information serves as an amendment to the original notification and provides the additional information requested.

1. *Page 2. Condition of use: For **adults**, take 2 capsules 2-3 times daily. Define the age of "Adults"*

Adults refer to persons 19 years and older.

2. *There is no warning on the label for individuals whose conditions, or medications might prevent them from taking this product.*

Warning: This product should not be taken by pregnant or lactating women without consulting a physician. Person experiencing flu or flu-like symptoms should stop taking this product.

Contraindications: none has been identified

3. *Names of all ingredients must have full Latin binomials including the author of the species designation. Other corrections on Table 1, page 2 are:
Spelling of "Glycyrrhizae" (should be Glycyrrhiza), deletion of "Common" from Common wheat and deletion of root from Licorice root.*

The following table replaces Table 1 of the original notification.

Table 1. Botanical ingredients in Sustotrong

| Latin Name | Common Name | Part used | mg/tablet |
|---|------------------|-----------|-----------|
| <i>Cordyceps sinensis</i> (Berg.) Sacc. | Cordyceps | Mycelium | 225 |
| <i>Triticum aestivum</i> L. | Wheat | Seed | 175* |
| <i>Glycyrrhiza grabra</i> L. | Licorice | Root | 10** |
| <i>Panax quinquefolius</i> L. | American ginseng | Root | 90* |

4. *What is the recommended duration of use?*

The effects are mild and may take weeks. One or two months of consumption is generally recommended.

We will modify our package label to reflect the changes indicated in 1, 2, 3 and 4.

5. *What is the new ingredient in this product?*

The new ingredient in this product is the cultured mycelia of *Cordyceps sinensis* (Berg.) Sacc. Even though another company (*P& Y American Dietary Supplement Inc.*) had submitted a notification on a similar ingredient (Docket number 95S-0316, RPT39), it is not clear if their ingredient is identical with our product, thus we have decided to submit this notification to FDA in accordance with CFSAN publication "New Dietary Ingredients in Dietary Supplements—Background for industry" updated September 10, 2001.

The natural Cordyceps is rare, thus it is difficult to harvest large quantities for medicinal use. Chinese scientists have extensively examined its life cycle and developed a technique to isolate fermentable strains (1). Sustotrong used strain Cs-4 for the propagation. The manufacturing process is as following:

- a. Expansion of culture from a single isolate to a small fermentor to a final fermentor of 20,000 liters.
- b. Filtrate through a flat-pressure filtrator. Mycelium is collected and lyophilized.
- c. The lyophilized mycelium is powdered and oven dried at
- d. Culture medium: g/liter

| | |
|---------------------------------|-------|
| Malt Extract | 24 g |
| Glucose | 20g |
| Yeast Extract | 5g |
| KH ₂ PO ₄ | 1.5g |
| Magnesium sulfate | 0.75g |
| Soy powder | 20g |
- e. Culture conditions:
 - Temperature:
 - pH:
 - Rotation speed: 300 rpm

6. *Even though there is no structure/function claims made on the package label, what is the intended use of this product?*

This product is used to promote general health and daily physical performance. It works to stimulate the immune functions and boost the energy level. Thus, it is especially useful for individuals under stress and general weakness due to illness or recovering from other medical conditions.

Many in vitro and animal experiments have demonstrated immune stimulatory, anti-oxidant and energy boosting effects of both natural and cultivated Cordyceps (1-4).

7. *Full reference citation for attachment 6 and 8*

For attachment 6.

- a. Physicians' Desk References, PDR 51 Edition, Page 2985, 1997. Medical Product Data Production Company, Montvale, NJ 07645-1742
- b. Chinese Herbal Medicine, Materia Medica, pp. 338-339, Revised Edition, Dan Bensky and Andrew Gamble, Eastland Press, Seattle, WA 98111, 1993

For attachment 8.

- a. Chinese Herbal Medicine, Materia Medica, pp. 358-359, Revised Edition, Dan Bensky and Andrew Gamble, Eastland Press, Seattle, WA 98111, 1993
- b. Oriental Materia Medica, A Concise Guide. pp. 596-597, Hsu, H-Y et al., eds. Oriental Healing Art Institute, Long Beach, CA 1986.

8. *Section C.a., Page. 2 indicates that the "Cordyceps was produced by fermentation in a biotechnologically aseptic environment". How does this fermented product compare to the traditional Cordyceps used in Chinese medicine in terms of its content and amount of use.*

Cordyceps, Chinese caterpillar fungus, is the fungus which grows on the carcass of the insect larvae, *Hepialus carians* Staudinger. The fungus is the portion which confers the biological activities (Ref. 1,2,4,5,6). In the current product, the fungus which is genetically identified by DNA fingerprint, is propagated by fermentation to achieve a better yield and lot-to-lot consistency. The mycelia is thus considered to have the same potency as those use in traditional medicine without the insect carcass.

In general, both natural Cordyceps and cultured mycelium are considered very safe among Chinese herbal medicine. In one report, IP injection of 5g/kg of Cordyceps into mice caused no fatalities, but does of 30-50 g/kg were universally fatal. (7). In another study, no deaths were seen 7 days or longer after mice were administered Cordyceps or mycelium at an oral dosage of 80 g/kg (2). Mutgenecity and teratogenicity studies of both natural and fermented products demonstrated no statistically difference from the negative control (2, 6,8).

In the traditional Cordyceps, the recommended dosage is 4.5-12 gram (7). A dose of 1 gram per serving 2-3 times per day was recommended by a similar product from *P& Y American Dietary Supplement Inc*. The amount recommended in our product is 550

mg/serving, 2 –3 times a day.

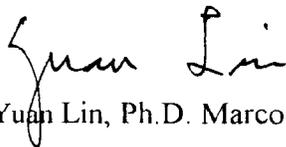
From the literature reports and the comparison to the dosages recommended by marketed products, this product can be reasonably expected to be safe.

9. *Provide a list of relevant scientific publications on both the natural Cordyceps and cultivated mycelia of Cordyceps particularly in areas related to safety.*

The following publications compare the activities and safety profiles of the natural and cultivated Cordyceps. The first two articles provide comprehensive reviews of Cordyceps with emphasis on the cultivated Cordyceps. Full-length articles are attached.

- Ref. 1. Zhu J-S, Halpern, GM, Johns K. The Scientific Rediscovery of an Ancient Chinese herbal Medicine: *Cordyceps sinensis*, part I. J Altern Complement Med 4:289-303, 1998
- Ref. 2. Zhu J-S, Halpern, GM, Johns K. The Scientific Rediscovery of a Precious Ancient Chinese Regimen: *Cordyceps sinensis*, part II. J Altern Complement Med 4:429-457, 1998
- Ref. 3. Li Y, Chen G-Z and Jiang D-Z. Effect of Cordyceps sinensis on erythropoiesis in mouse bone marrow. Chinese Med J 106:313-316, 1993
- Ref. 4. Dai G, Bao T, Xu C, Cooper R and Zhu J-S. CordyMax Cs-4 Improves steady state bioenergy status in mouse liver. T. Altern Complement Med 7:231-240, 2001.
- Ref. 5. Li SP, Li P, Dong TTX and Tsim KWK. Anti-oxidation activity of different types of natural *Cordyceps sinensis* and cultured *Cordyceps* mycelia.
- Ref. 6. US Patent 5948404, Inventors, Tajetini N, Tsunoo A and Itoh H. Healthful composition obtained from the hot water extract of Cordyceps sinensis mycelia, 1999. (Due to the length of the full text, only first 12 pages were included).
- Ref. 7. Chinese Herbal Medicine, Materia Medica, pp. 338-339, Revised Edition, Dan Bensky and Andrew Gamble, Eastland Press, Seattle, WA 98111, 1993.
- Ref. 8. Kong X, Jiang B, Wang H, Yin X, Tang, Y, Ma Z, Shen J, Zhang H and Xiao Z. Toxicological study of Cordyceps sinensis cultivated by artificial fermentation on its safety evaluation II Mutagenicity study. J Capital Inst Med 16:256-258, 1995

Sincerely Yours



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