

Memorandum

Date:

SEP 13 2005

From:

Consumer Safety Officer, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject:

75-Day Premarket Notification of New Dietary Ingredients

To:

Dockets Management Branch, HFA-305

Subject of the Notification: ACAPHA

Firm: Global Cancer Strategies Ltd.

Date Received by FDA: June 27, 2005

90-Day Date: September 25, 2005

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria Lutwak

19955-0316

RPT296



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

SEP 9 2005

Dr. T. P. Chiang
Global Cancer Strategies Ltd.
113-990 Beach Avenue
Vancouver, British Columbia V6Z 2N9
Canada

Dear Dr. Chiang:

This is to inform you that the notification, dated June 23, 2005, that you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on June 27, 2005. Additional information was received on June 28, 2005. Your notification concerns the substance that you call "ACAPHA" that you intend to market as a new dietary ingredient for use in dietary supplement products.

According to your notification, "ACAPHA" will be marketed as a dietary supplement product, in tablet form, called "Prohibit-Rx". Each tablet will contain 600 mg of "ACAPHA". Your notification further states that the recommended serving level will be 3 tablets daily, as follows: "the tablets should be consumed three times, one tablet at a time orally with water or liquid, before meals. The product is intended for use by healthy adult males and females..."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b (a) (2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f) (1) (B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "ACAPHA" will reasonably be expected to be safe.

Your notification fails to adequately describe your new dietary ingredient, "ACAPHA". For example, the ratio of herb material to solvent is not stated in the manufacturing process. The degree to which the product has been concentrated cannot be determined since your notification did not provide the initial ratio of herb material to solvent. In addition, according to your notification, the product will be standardized to the content of the alkaloid, matrine, which appears to be present in only one (1) of the six (6) botanicals in your extraction mixture. Thus it is unclear to what extent matrine contributes to the components of your final product.

Although your notification provided history of use for the botanical materials from which "ACAPHA" is manufactured as traditional herbal medical products, you did not provide evidence of the history of use of these botanicals or of "ACAPHA" as food. It is unclear how the history of use of these botanicals as drugs is relevant to the evaluation of the safety of a dietary supplement product containing "ACAPHA".

In addition, the relationship of the test materials used in the animal safety studies to the new dietary ingredient that you intend to market is unclear. For example, the materials used in tests in mice, rats and dogs are described as having been produced by at least two different companies, neither of which appears to be the same as Central Pharmaceutical Co., Ltd of Tianjin China, the company you have identified as the manufacturer of your new dietary ingredient. It is unclear how the test substance is qualitatively or quantitatively similar to the test substances described in the information that you rely on for the safety for your new dietary ingredient called "ACAPHA".

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "ACAPHA" when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

From the information submitted in your notification, it appears that "ACAPHA" is marketed outside of the United States to treat medical conditions. Please be aware that under 21 U.S.C. 321(g)(1)(B), if a product is implicitly or expressly represented as being intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease, it may be subject to regulation under the drug provisions of the Act. If you intend to make claims or representations of this nature, you should contact FDA's Center for Drug Evaluation and Research (CDER).

Your notification will be kept confidential for 90 days after the filing date of June 27, 2005. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

Page -3- Dr. Chairng

If you have any questions concerning this matter, please contact Linda S. Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'S. Walker', written over a horizontal line.

Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety and Applied Nutrition



Global Cancer Strategies Ltd. Preventive Health Division

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

June 23, 2005

Dear Sir/Madam:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, Global Cancer Strategies Ltd., Preventive Health Division, located at 113-990 Beach Avenue, Vancouver, BC, Canada V6Z 2N9, wishes to notify the Food and Drug Administration that it will market a new dietary supplement, ProhibitRx*, prepared from six commonly available botanicals: namely, Vietnamese Sophora (*Sophora tonkinensis* Gapnep), bistort (*Polygonum bistorta*), heal all (*Prunella vulgaris* L.), perennial sowthistle (*Sonchus brachyotus*), dense fruit dittany (*Dictamnus dasycarpus* Turcz), and air potato (*Dioscorea bulbifera*). Enclosed please find two 3 copies of this notification. Details of concentrations and content of the product, conditions of use stated in the labeling, and evidence of safety are documented in the enclosed attachment.

The dietary supplement will contain 600mg of ProhibitRx* in film coated tablet form with a suggested daily dose of 1.8g, 600mg/tablet to be taken three (3) times per day.

ProhibitRx* contains six herbs that have been used as herbal medicine or food for centuries in Asia and Europe. Safety and toxicity studies of the supplement have been performed in rats, mice, dogs and healthy volunteers. They include mutagenicity, acute and chronic toxicity tests in rodents and dogs, and tolerance of healthy human volunteers. The maximum tolerable daily dose is greater than 20g/kg in mice, 833 times the intended human dosage. Healthy volunteers taking 4.8g of ProhibitRx* daily (2.7 times the recommended dose) for as long as 4 weeks did not reveal any adverse reaction. Safety and toxicity studies showed that ProhibitRx* did not have accumulative toxicity in animals, nor was it mutagenic in bacteria and mice.

Attached please find the detailed information which establishes that this dietary supplement, when used under the conditions suggested in the label, is expected to be reasonably safe. Please direct all correspondence to me if you have any questions regarding this matter.

Very truly yours,

Dr. T. P. Chiang
CEO

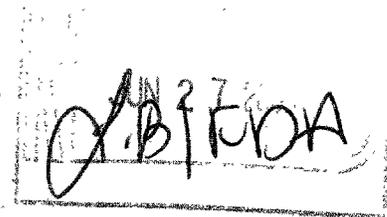
*The proposed new dietary ingredient is labeled ProhibitRx to prevent confusion with the trade name ACAPHA used in all the tests and studies in the enclosed documents and references



Global Cancer Strategies Ltd. Preventive Health Division

Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
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5100 Paint Branch Parkway
College Park, MD, 20740-3835
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June 23, 2005



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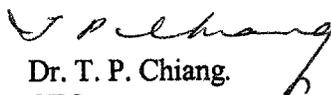
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Very truly yours,


Dr. T. P. Chiang
CEO

2605-3859

The proposed new dietary ingredient is labeled ProhibitRx to prevent confusion with the trade name ACAPHA used in all the tests and studies in the enclosed documents and references

New Dietary Ingredient Notification

Product name: ACAPHA

Global Cancer Strategies Ltd.

Preventive Health Division

Vancouver, British Columbia, Canada

Date: June 23, 2005

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1. Manufacturer

The new dietary ingredient is being produced by Global Cancer Strategies Ltd., Preventive Health Division Vancouver, British Columbia, Canada, intended to be distributed in the United States. ACAPHA is a traditional Chinese herbal product, prepared from six Chinese herbs, that was approved by the Chinese State Food and Drug Administration (SFDA) for the treatment of esophageal dysplasia and stomach problems. It is manufactured by Central Pharmaceutical Co. Ltd., a Chinese GMP pharmaceutical manufacturer, addressed at 1 Fujin Avenue, Beichen District, Tianjin, China.

2. Name of the New Dietary Ingredient

The name of the new dietary ingredient is ACAPHA. Its Chinese name is Zeng Sheng Ping. The Binominal Latin names of the herbs used in the preparation of ACAPHA are:

Latin name: *Sophora tonkinensis* Gapnep

Family: leguminosae

Plant parts used: dried roots and taproot

Latin name: *Polygonum bistorta* L.

Family: polygonaceae

Plant parts used: dried rhizome

Latin name: *Prunella vulgaris* L.

Family: labiatae

Plant parts used: dried flower stem

Latin name: *Sonchus brachyotus* DC

Family: valerianaceae

Plant parts used: dried whole plant

Latin name: *Dictamnus dasycarpus* Turcz

Family: rutaceae

Plant parts used: dried root bark

Latin name: *Dioscorea bulbifera* L.

Family: dioscoreaceae

Plant parts used: dried rhizome

Sophora tonkinensis is considered the major ingredient in ACAPHA

3. Description of ACAPHA

ACAPHA is a traditional Chinese herbal supplement, prepared from six herbs in accordance with Chinese GMP regulations. Historically, it has been used in traditional Chinese medicine for its beneficial effects on epithelial tissues in association with the GI and respiratory tract. At high doses ACAPHA is approved by the Chinese State Food and Drug Administration (SFDA) for the treatment of esophageal dysplasia and dysplasia of the cardiac region of the stomach.¹

3.1 Known Major Chemicals in Each Botanical

<i>Sophora tonkinensis</i> ²⁻⁵	<i>Polygonum bistorta</i> ⁶⁻⁸	<i>Prunella vulgaris</i> ⁹⁻¹¹
/	/	/

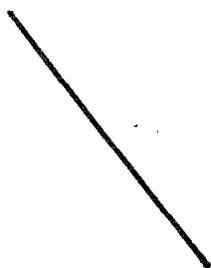
<i>Sonchus brachyotus</i> ¹²⁻¹⁴	<i>Dictamnus dasycarpus</i> ¹⁵⁻¹⁷	<i>Dioscorea bulbifera</i> ¹⁸⁻²¹
/	/	/

3.2 Physical and Chemical Characteristics

The known major bio-active chemical compounds (and their respective natures) present in ACAPHA are listed in the table below.

Compound	Nature
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

Using gas chromatography-mass spectroscopy (GCMS) _____ has been identified as the major alkaloid in ACAPHA (see figure).

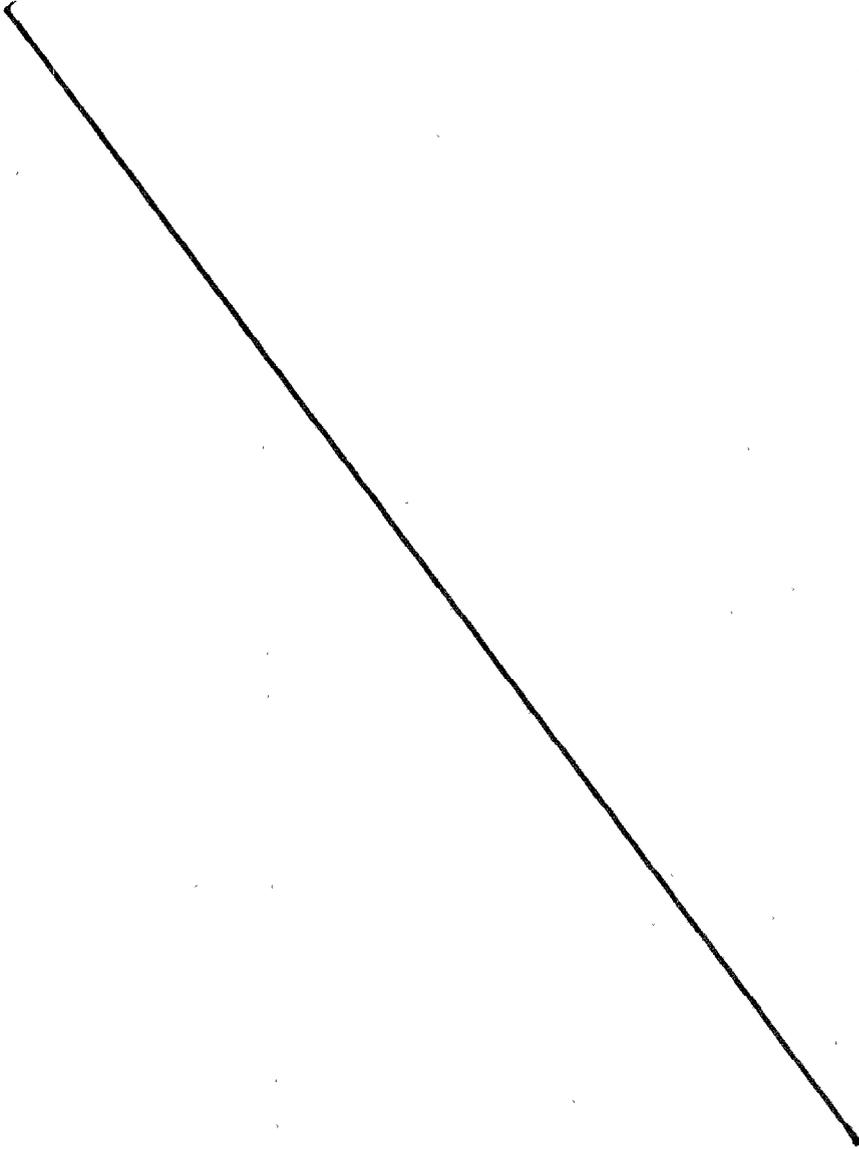


PAGE 6

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3.3 Manufacturing Method



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4. Level of Ingredients in ACAPHA

Each 600mg tablet of ACAPHA is represented by

<i>Sophora tonkinensis</i>	_____
<i>Polygonum bistorta</i>	_____
<i>Prunella vulgaris</i>	_____
<i>Sonchus brachyotus</i>	_____
<i>Dictamnus dasycarpus</i>	_____
<i>Dioscorea bulbifera</i>	_____

4.1 Recommended daily dose

The recommended total daily dose is 1.8g, 3 x 600 mg tablets/day.

4.2 Administration recommended

The tablets should be consumed three times, one tablet at a time orally with water or liquid, before meals.

4.3 Suggested labeling of new dietary supplement

The film coated tablets are packed in amber HDPE bottles, the top sealed with aluminum foil seal and closed with white plastic cap at 80 tablets per bottle and put in a carton box. The tablets are to be stored at ambient temperature between 15-30 degree Celsius. The product will be labeled as a dietary supplement for healthy cellular and respiratory function and for a healthy aero-digestive function. It will be targeted towards adults who are concerned with the increase in environmental pollutants in water, food and air.

4.4 Recommended Conditions of use

The product is intended for use by healthy adult males and females who are seeking to supplement their diet with herbal supplement to support the health of their epithelial tissues such as the oro-pharyngeal and respiratory tissues, i.e., support normal respiratory function in a smoke-rich environment, support respiratory health for those exposed to second hand

smoking., supports body's ability to cope with a polluted environment, may help minimize the risks to long-term health posed by exposure to environmental toxins.

5. History of Use

The six herbs that make up ACAPHA have a long history of use in traditional Chinese medicine.

Sophora tonkinensis root is believed to have the function of removing toxic heat, promoting subsidence of swelling and soothing sore throat. It has a bitter taste and a cold property, acting on the lung and stomach channel. According to the Chinese Materia Medica, the root of *Sophora tonkinensis* (Shan Dou Gen) contains alkaloids such as matrine and oxymatrine, and flavonones such as sophoranone. A wide range of benefits is attributed to its main components matrine and oxymatrine and has been used in the treatment of leucopenia, arrhythmia, bronchial asthma and chronic asthmatic bronchitis. While a few side effects such as nausea, vomiting, dizziness and headache are attributed to the herb, the water extract is reported to be relatively non-toxic³. The quantity for consumption of *Sophora tonkinensis* recommended by Chinese Pharmacopoeia is 3-6gram per day while the consumption dose of herb in ACAPHA is equivalent to 2.52 crude herb per day. This quantity is well below the recommended dose and therefore, is expected reasonably safe and unlikely to cause side effect when used under the conditions claimed on the label. *Sophora tonkinensis* is currently sold in the United States and is listed in the American Herbal Products Association's book Herbs of Commerce.²⁷

Polygonum bistorta is thought to dispel heat, remove toxins, resolve phlegm and disperse accumulated masses. It has a bitter flavor and works via the liver meridian. The Oriental Materia Medica reports that the herb has antibacterial, anticancer, and antitussive benefits.⁶ *Polygonum bistorta* is currently sold in the United States and is listed in the American Herbal Products Association's book Herbs of Commerce.²⁷

Prunella vulgaris is described by the Chinese Materia Medica to have a pungent and bitter taste and a cold property. It acts on the liver and gallbladder channels and quenches liver-fire,

counteracts inflammation of the eye, reduces nodulation and induces subsidence of swelling. It has been used traditionally in hypertension due to 'hyperactivity of the liver' and in shrinking lymph nodes associated with tuberculosis.⁹ *Prunella vulgaris* is currently sold in the United States and is listed in the American Herbal Products Association's book on Herbs of Commerce.²⁷

Sonchus brachyotus is described in the Oriental Materia Medica to have a bitter, pungent flavor; mild and having cold property. It acts on the stomach and large intestine channels and liver meridians. Traditional uses include removal of toxic heat, elimination of furuncles, pus drainage, phlegm removal and invigoration of blood circulation.¹² *Sonchus brachyotus* is available in the United States as part of a multi-herb preparation for irritable bowel syndrome, sold in the trade name of Bowelsoothe.²⁸⁻³⁰ Along with its synonym *Sonchus arvensis* L., *Sonchus brachyotus* is used as the same herb in the name of Bai Jiang Cao. The traditional use of Bai Jiang Cao has been authorized by the Chinese government at a dose of 9-15g dry herb (reference #1-2). Both *Sonchus arvensis* and *Sonchus brachyotus* have the same English name of Perennial sowthistle and have a long history of use as food in Asia, Europe and North America (reference #3-7). The quantity of *Sonchus* consumed as food in the form of fresh vegetable is 50 gram per serving while for medicinal use is recommended at 9-15 gram dry herb. As one of the six ingredients in ACAPHA, the dose of *Sonchus brachyotus* present in 1.8g is equivalent to 2.52 gram dry herb per day. This quantity is about one fifth to one third of recommended dose in the literature. Based on the available information on *Sonchus brachyotus* mentioned above, it is considered reasonably safe when used as one of the ingredients in ACAPHA although *Sonchus brachyotus* is the only herb not listed in the American Herbal Products Association's book Herbs of Commerce²⁷

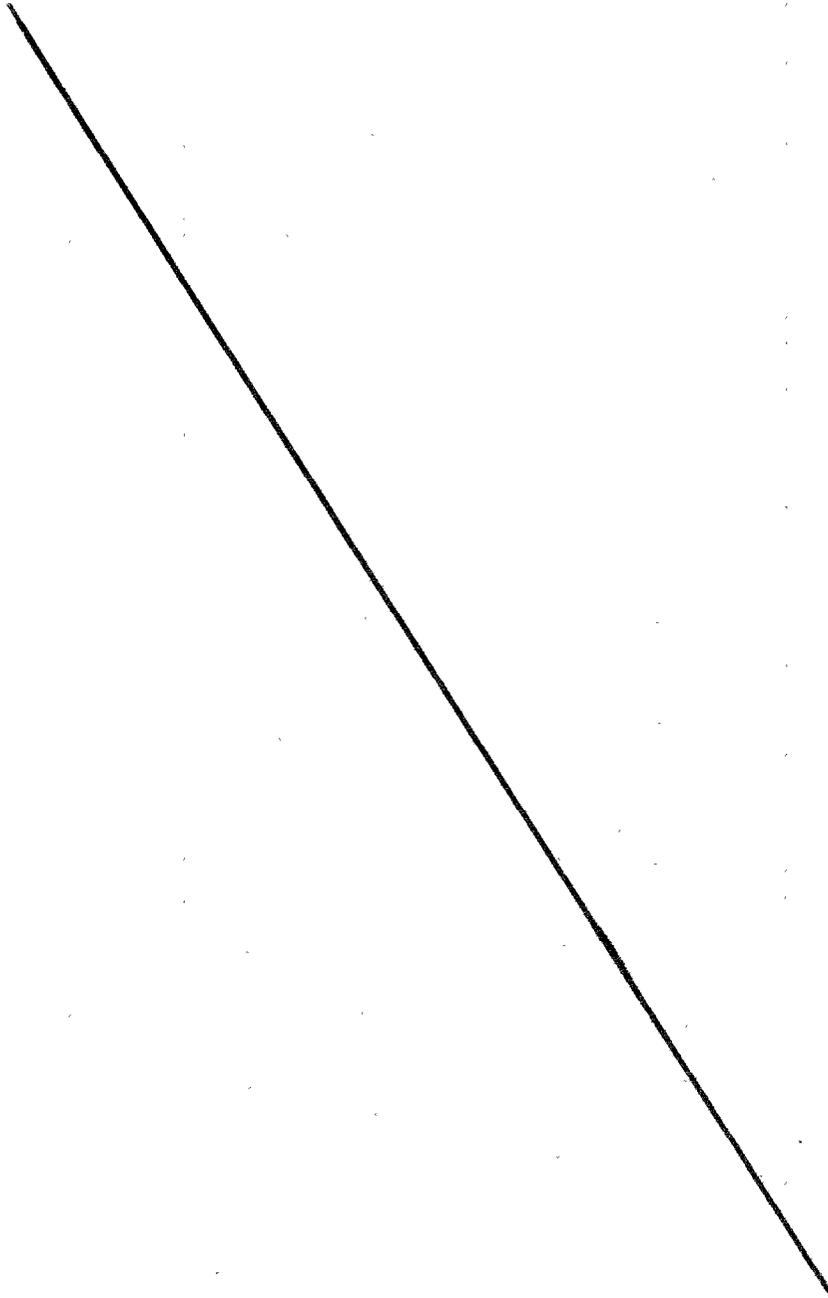
Dictamnus dasycarpus is described in the Chinese Materia Medica as having a bitter taste and a cold property. It acts on the spleen, stomach and urinary bladder channels and has the functions of removing damp-heat, and dispelling wind and stopping itch. It has been traditionally used in skin inflammation with yellowish discharge, eczema with itching and

jaundice with dark urine.¹⁶ *Dictamnus dasycarpus* is currently sold in the United States and is listed in the American Herbal Products Association's book *Herbs of Commerce*.²⁷

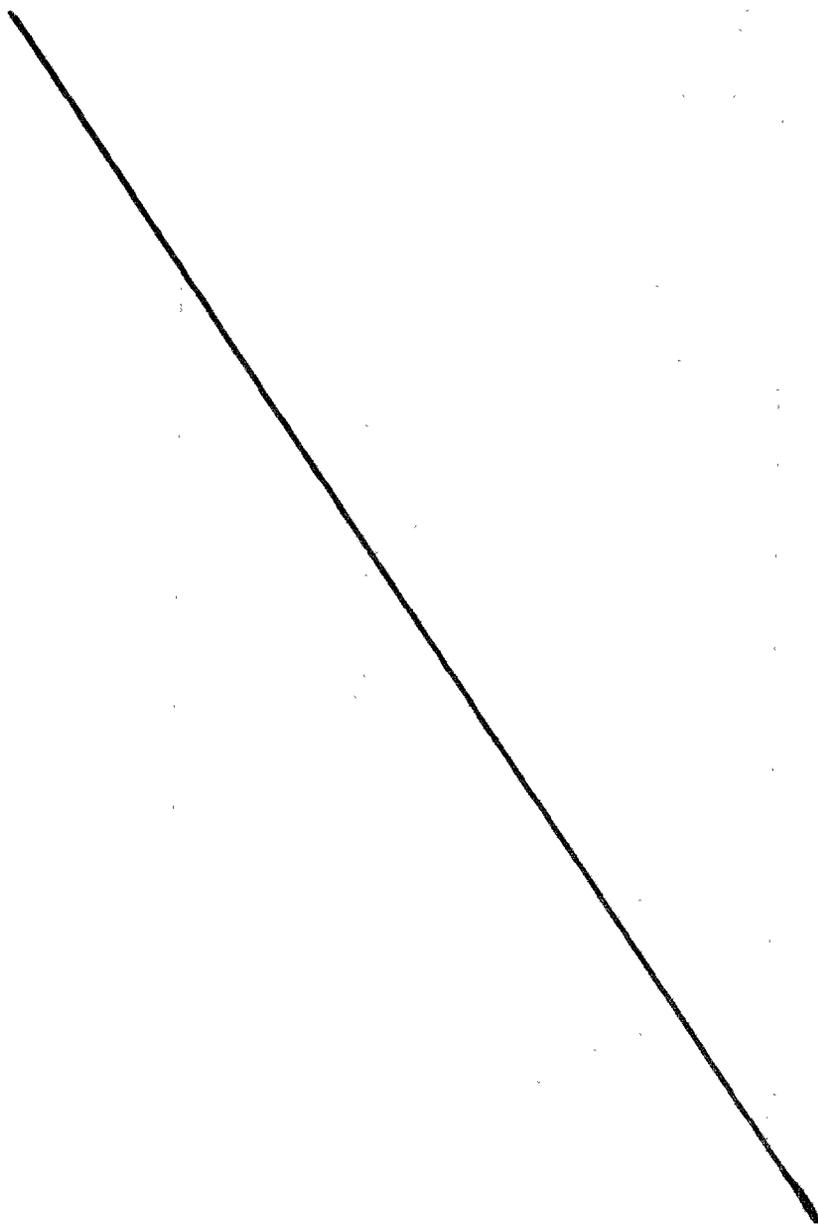
Dioscorea bulbifera is described in the *Oriental Materia Medica* to have bitter taste and neutral properties. It acts via the liver and heart meridians and has been used traditionally to resolve phlegm, control cough, disperse goiter and control bleeding. It has antibacterial and antifungal properties.²⁰ *Dioscorea bulbifera* is currently sold in the United States and is listed in the American Herbal Products Association's book *Herbs of Commerce*.²⁷

The rationale of using a combination of agents for in traditional medicine is not new. Combinations of two or more agents with different presumed mechanisms of activity are often thought to provide synergistic or additive activity. Such improved activity may allow some or all of the agents to be administered at lower doses, thereby reducing potential toxicity while improving efficacy.

5.1 Evidence of Safety



5.2 Toxicology



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6.0 Conclusion

Based upon the toxicology studies, we conclude that ACAPHA is considered to be safe at the recommended maximum daily oral dose of 1.8g, 600 mg tablet three times a day.

7.0 Appendix

1. Copy label indicating approved usage of ACAPHA by Chinese State Drug Administration.
2. Bensky, D., Gamble, A., *Chinese Herbal Medicine: Materia Medica*. Seattle, Washington, Eastland Press, Inc.; c1993, pp.103-4
3. Hsu, H., Chen, Y., Shen, S., Hsu, C., Chen, C., *Oriental Materia Medica*. New Canaan, CT. Keats Publishing, Inc.; c1986 pp.236-7
4. Zhu, You-Ping, *Chinese Materia Medica*. The Netherlands: Gordon & Breach Publishing Group; c1998 pp.202-4
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21. Bensky, D., Gamble, A., *Chinese Herbal Medicine: Materia Medica*. Seattle, Washington, Eastland Press, Inc.; c1993, pp.189
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23. Heinemann, T., Axtmann, G., Von Bergmann, K., Comparison of intestinal absorption of cholesterol with different plant sterols in man. *European Jnl of Clin Investigation* 1993;23:827-831
24. Manufacturing Process for ACAPHA
25. Drug stability testing results and conclusion/batch consistency and stability
26. Stability Testing
27. McGuffin, M. Managing Editor., *Herbs of Commerce*, 2nd ed. American Herbal Products Association; c2000 pp. 56, 117, 120, 138
28. Bensoussan, A., Talley, N.J., et al Treatment of irritable bowel syndrome with Chinese herbal medicine *JAMA* 1998; 280:1585-1589
29. Yan, Q.M., Chen Y., et al Study on the treatment of irritable bowel syndrome with a Chinese herbal medicine *Chinese Journal of Internal Medicine* 1997; 3(1):30-34
30. Wang, B.H., Ren, S.P., et al BowelSoothe in the treatment of IBS and chronic non-specific ulcerative colitis @ www.neopharmica.com/IBS20.htm
31. Registry of Toxic Effects of Chemical Substances from the US National Institute for Occupational Safety and Health @ <http://ccinfoweb.ccohs.ca/rtecs/search.html>
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35. _____

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37. Yan, S., Yu, G.Q., *Integrated Chinese and Western approach in cancer prevention and therapy*. Peking Medical University and Peking Union Medical College Press; c1995

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8.0 Reference

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6. Launert. E. *Edible and Medicinal Plants*. Hamlyn 1981 ISBN 0-600-37216-2
7. Facciola. S. *Cornucopia -A Source Book of Edible Plants*. Kampong Publications 1990 ISBN 0-9628087-0-9