SUMMARY OF DATA FOR CHEMICAL SELECTION

Ginseng and Ginsenosides
50647-08-0

BASIS OF NOMINATION TO THE CSWG

Ginseng and ginsenosides are presented to the CSWG as part of a review of botanicals used as dietary supplements. Worldwide, ginseng production is a $3 billion industry. Asia is the largest market; 80 percent of American ginseng is exported to Asia. Ginseng is also a popular herbal remedy in the US, with five to six million persons using it even before the recent boom in the herbal supplement industry. Although ginseng root is commonly used, a standardized ginseng extract, Ginsana™, with annual sales of over $40 million, is the most popular encapsulated form.

Numerous reports of adverse effects from products containing ginseng have been filed with the US Food and Drug Administration (FDA). The literature also documents "ginseng abuse syndrome" among regular users. The chronic effects of ginseng are not well characterized; studies of some components suggest anticarcinogenic activity.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

The American Botanical Council provided monographs on Asian Ginseng (Botanical Series - 303) and American Ginseng (Botanical Series - 308) to assist with this project and indicated that their study of ginseng products will not be available until next year.

SELECTION STATUS

ACTION BY CSWG: 9/16/98

Studies requested:

Parallel testing of Ginsana™ and RB1 ginsenoside for the following tests:

- Carcinogenicity studies
- Genotoxicity including standard mammalian assays and the *in vivo* micronucleus test
- Reproductive toxicity

Priority: High

Rationale/Remarks:

- Significant human exposure

- One of the most popular herbal supplements in the US market; Ginsana™ is a standardized extract that controls half of this market

- Little information on toxicity available

- Active ingredients may be dammaranes; RB1 ginsenoside is a commercially available dammarane found in ginseng

- Possibility that these compounds may have anticarcinogenic activity should also be considered

CHEMICAL IDENTIFICATION

CAS Registry No.:	50647-08-0
Chemical Abstract Service Names:	Prosapogenin (Ginseng) (9CI)
Synonyms:	Ginseng, ginseng root extract, ginseng root neutral saponins, ginseng root tincture, ginsengwurzel extract, panax, panax ginseng, panax schinseng, prosapogenin
Botanical Names:	The *Panax* genus contains about six species native to eastern Asia and two native to eastern North America (Foster, 1996a,b). *Panax ginseng* C.A. Meyer (Asian, Chinese, Korean, or Oriental ginseng) and *Panax quinquefolius* L. (American ginseng) are most commonly used in nutraceuticals.

Description: Ginseng is a perennial aromatic herb with a short underground stem (rhizome) associated with a fleshy white root. Its root system consists of the primary root and its branches and of some adventitious roots developed from the rhizome. The above-ground part of the plant is a 30-70 cm single stem that dies annually (Sticher, 1998). The plant blooms after two years, reaches maturity after five and is harvested in its sixth year (Hook, 1979). True ginsengs are members of the genus *Panax* in the *Araliaceae* family. In addition to *Panax ginseng* and *Panax quinquefolius,* other ginsengs include *Panax japonicus* (Japanese ginseng), *Panax notoginseng* (Sanqui or Tienqi ginseng), *Panax elegantior* (Pearl ginseng), *Panax pseudoginseng* (Himalayan ginseng), and *Panax zingiberensis* (ginger ginseng) (Ocollura, 1997).

Some plants are not a true ginseng (i.e., different genus or family), but they have the term ginseng in their common names. These include Siberian ginseng (*Eleutherococcus senticosus*) which is widely used in dietary supplement preparations, Prince ginseng (*Pseudostellaria heterphylla*), Indian ginseng (Ashwangdha), and Brazilian ginseng (*Pfaffia paniculata*) (Ocollura, 1997). Except where it is impossible to distinguish the form of ginseng, these products are not discussed further.

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Technical Products and Impurities: Despite the growing market for extracts and powders, the most popular ginseng products remain the white and red roots. Ginseng roots may be graded by size. For example, Heaven 15 is a grade of Korean ginseng which means 15 roots fit into a standard ginseng container. Heaven 30 means 30 roots fit into the same container. The larger the number, the smaller and less valuable the root (Ocollura, 1997). Table 1 lists various ginseng products and their availability.

Table 1. Some Ginseng Products Available in the US

Product	Manufacturer or Distributor
American ginseng	Bio-Botanica, Inc., Mini Star International, Inc., Pharmline, Inc., Sigma
Ginseng extract	Allchem Industries, Inc., Amax Industries, Inc., American Ingredients, Inc., Anmar International, Ltd., Ashland Chemical Company, China Tech, Inc., DNP International Co., Inc., Extractsplus, Frutarom Meer Corporation, International Sourcing, Inc., Kowa American Corp., M.W. International, Inc., Mini Star International, Inc., Motherland Herb-Pharm, Inc., Pharmline, Inc., Pro-Pharm, Inc., and RIA International
Ginseng powder	American Ingredients, Inc., Ashland Chemical Company, Belmont Chemicals, Inc., Botanicals International., Inc., a division of Zuellig Botanicals, Inc., Kowa American Corp., Maypro Industries, Inc., Mini Star International, Inc., Motherland Herb-Pharm, Inc., RIA International, and The Whole Herb Co., Inc.
Ginseng root	American Ingredients, Inc., Botanicals International, Inc., Herbarium, Inc., and Mini Star International, Inc.
Ginseng root extract	American Ingredients, Inc., Bio-Botanica, Inc., Extractsplus, Frutarom Meer Corporation, Mini Star International, Inc., Motherland Herb-Pharm, Inc., and Quality Botanical Ingredients, Inc.
Korean ginseng	American Ingredients, Inc., Ashland Chemical Company, M.W. International, Inc., Mini Star International, Inc., Motherland Herb-Pharm, Inc., Pharmline, Inc., and Pro-Pharm, Inc.
Panax ginseng	American Ingredients, Inc., Bio-Botanica, Inc., China Tech, Inc., Mini Star International, Inc. , and Motherland Herb-Pharm, Inc.
Ginseng glucosides	DNP International Co., Inc. and Sigma (95% pure, prepared from American ginseng root; contains a mixture of ginsenoside-Rb_1 [41753-43-9], ginsenoside Rc [11021-14-0], and ginsenoside-Re [51542-56-4] .

Sources: McCoy, 1998; Sigma, 1998

Ginseng is an expensive crop to produce so adulteration or substitution with cheaper products occurs (Ocollura, 1997). Some products sold as ginseng have contained *Mandragora officinarum*, with hyoscine, *Rauwolfia serpentina*, with reserpine, and *Cola*, with caffeine; other commercial preparations were found to be adulterated with phenylbutazone and aminopyrine

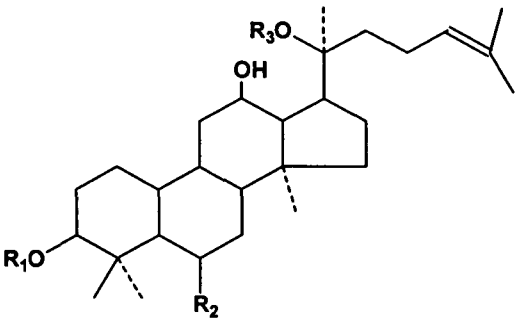
(Chandler, 1988). To protect its interests in the Hong Kong market, the Ginseng Board of Wisconsin organized a labeling system for genuine American ginseng products (Proctor, 1996). A comprehensive ginseng evaluation program of hundreds of commercial ginseng products was initiated by the American Botanical Council to determine if adulteration has occurred; in June 1998, the American Botanical Council confirmed that the results will not be available for another year (Proctor, 1996; Ocollura, 1997; American Botanical Council, 1998).

Chemical Composition: Several classes of compounds have been isolated from ginseng root. These include triterpene saponins, essential oil-containing polyacetylenes and sesquiterpenes, polysaccharides, peptidoglycans, nitrogen-containing compounds, and various ubiquitous compounds such as fatty acids, carbohydrates, and phenolic compounds (Sticher, 1998).

The chemical constituents of ginseng believed to contribute to its pharmacological effects are triterpene saponins. These compounds are named ginsenosides Rx according to their mobility on thin-layer chromatography plates, with polarity decreasing from index "a" to "h". This property is a function of the number of monosaccharide residues in the sugar chain. The aglycons are protopanaxadiol and protopanaxatriol; both have a dammarane skeleton. So far, 31 ginsenosides have been isolated from the roots of white and red ginseng. They can be categorized into three groups depending on their aglycons: protopanaxadiol-type ginsenosides, protopanaxatriol-type ginsenosides, and oleanolic acid-type saponins (Sticher, 1998).

Nearly all dammarane ginsenosides isolated from white ginseng root are derivatives of 20S protopanaxadiol and 20S protopanaxatriol (see table on page 6). Almost all the ginsenosides isolated from white ginseng are also found in red ginseng; however, some ginsenosides (20R Rg_2; 20R Rh_1; Rh_2, Rs_1, Rs_2, Q-R_1, and NG-R_1) are characteristic saponins for red ginseng. The 20R compounds are degradation products formed by heating and hydrolysis during steaming (Sticher, 1998).

The structures of the more common ginsenosides are shown below.



20(S)-protopanaxadiols

Ginsenoside	R_1	R_2	R_3
Rb_1	glc-glc	H	glc-glc
Rb_2	glc-glc	H	glc-ara(p)
Rc	glc-glc	H	glc-ara(f)
Rd	glc-glc	H	glc

20(S)-protopanaxatriols

Ginsenoside	R_1	R_2	R_3
Re	H	-O-glc-rha	glc
Rf	H	-O-glc-glc	H
Rg_1	H	-O-glc	glc
Rg_2	H	-O-glc-rha	H
Rh_1	H	-O-glc	H

glc = glucose; ara(p) = arabinose in pyranose form; ara(f) = arabanose in furanose form; rha = rhamnose
Sources: Gillis, 1997; Sticher, 1998

Panax ginseng, Panax quinquefolium, and *Panax notoginseng* are closely related chemically and taxonomically. Generally, they contain total ginseng saponin below 0.1 percent, and the sapogenins constitute chiefly dammarane-type triterpenes, with a higher content of panaxadiol and panaxatriol, but a very low content of oleanolic acid as sapogenin. *Panax notoginseng* contains no oleanolic acid sapogenin. The total saponin content of the remaining *Panax* species is 10-20 percent, and oleanolic acid is the major sapogenin (Peigen, 1989).

The stems, leaves, flowers, flower-buds, and fruits contain more ginseng saponins than the ginseng root. The underground part contains higher amounts of ginsenosides Rb_1, Rc, and Rg_1, while the above-ground parts contain higher amounts of ginsenosides Rd, Re, and Rg_1 (Peigen, 1989).

EXPOSURE INFORMATION

Environmental Occurrence: Several *Panax* species are indigenous to the Northern Hemisphere, from the eastern Himalayas through China and Japan to North America. *Panax quinquefolius* is found on rich, rocky, shaded, cool slopes of eastern North America, from Quebec to Manitoba, south to northern Florida, Alabama, and Oklahoma. Its peak abundance is in the Cumberland Gap region of southern Appalacia. Wild ginseng is now considered a threatened, rare, or endangered species in many areas due to overzealous harvest of the root for commercial purposes. Because of continual harvest and use over thousands of years, the natural supply of ginseng root was exhausted in China long ago. (Lewis & Zenger, 1982; Eastman, 1976; Sticher, 1998).

When American ginseng was initially exported in the early eighteenth century, wild *Panax ginseng* had already become extremely scarce in China. The relative abundance and quality of wild American ginseng opened the way for development of cultivated American ginseng as an export crop in the twentieth century (Hsu, 1979). Although wild-harvested root is still a US export, ginseng is now cultivated in China, Korea, Japan, and North America. Ginseng is an especially important crop in the state of Wisconsin (Hsu, 1998; Sticher, 1998).

Production and Producers: *Production Methods.* Ginseng is propagated from seeds harvested from ripe fruits of 4- to 5-year old plants. The seeds germinate in 18-20 months, and the seedlings may be transplanted to permanent beds when they are one or two years old. Four to six years later, the root is harvested. Because wind, rain, and direct sun can be harmful, the ginseng plants are grown within an artificial shelter. Ginseng is harvested between August and October when the above ground portion turns yellow (Sticher, 1998).

White ginseng is prepared by removing the small and hairy roots, scraping the outside skin off the main root and drying it in the sun, over charcoal, or in an oven. Red ginseng is prepared by removing all soil from the root, cutting off the hairy and branch roots, and

brushing the skin until it looks white. The root is then steamed for three hours, dehydrated in a dry room, and dried in the sun (Hook, 1979).

An efficient tissue culture regeneration system may be an alternative to seeding. Such a system would allow asexual propagation of the crop, the selection and propagation of uniform germplasm, and manipulation of the genetic make-up of the plant (Proctor, 1996). Cultured ginseng products derived from cell suspension culture of *Panax ginseng* have been produced commercially by Nitto Denko Co. in Japan since 1990 with net sales of $3 million in 1995 (Fu, 1998).

Production/Import Levels. Worldwide, ginseng production is a $3 billion industry with the amount estimated to be 22,154,000 pounds in 1993. South Korea and China each produced about 10,000,000 pounds, the US produced at least 1,384,000 pounds, Japan produced 76,000 pounds, and Canada produced 694,000 pounds. Figures for North American ginseng production in 1993 and 1994 are presented in Table 2 (Proctor, 1996; Chang, 1998).

Table 2. North American Ginseng Production for 1993 & 1994 (dry weight, lbs)

State/Province	1993	1994
Wisconsin	1,284,000	1,472,000
Ontario	510,000	648,000
British Columbia	184,000	328,000

Adapted from Proctor, 1996

In 1995, 1,552,324 pounds of cultivated ginseng root, valued at $44,905,434, was exported from the US, while 358,260 pounds of wild-harvested root, valued at $31,457,267, was exported (Pumphrey, 1996). Much of the North American ginseng is marketed directly from the farm to ginseng brokers in Hong Kong, the major importer, distributor, processor, and retailer of ginseng. Over 80 percent of ginseng grown in North

America is shipped to the Hong Kong market as is much of the ginseng from China and Korea (Proctor, 1996).

Redistribution of ginseng from Hong Kong is world-wide with major destinations being Taiwan, Japan, Malaysia, Singapore, and the US There has also been a strong European market for ginseng since the 1960s, with well-established markets in Scandinavia, Poland, Germany, Spain, Holland, Belgium, the U.K., France, and Italy. Figures for US imports of ginseng are given in Table 3 (Proctor, 1996).

Table 3. US Imports of Ginseng for Consumption for 1997*

Country	Cultivated ginseng roots (lb)	Wild ginseng roots (lb)
World total	1,134,649	439,551
Brazil	7,718	5,907
Canada	99,416	304
China (mainland)	835,744	353,477
Federal Republic of Germany	1,535	662
Hong Kong	138,529	52,680
Japan	7,260	-
Republic of Korea	43,794	8,880
Mexico	187	17,640
Singapore	88	-

*Includes species other than *Panax*.
Source: Import Administration, 1998

Many Canadian and US ginseng growers and licensed wild ginseng dealers sell their products directly to consumers. Most products are small, medium, or large roots, either fresh or dried. Some have also expanded their product lines to include capsules, powder, extracts, root slices, tea bags, candy, lotions, and soaps (Carl, 1997; Hsu, 1998; Woods Grown, 1998).

Use Pattern: Ginseng, alone, or in combination, is a popular herbal remedy. Ginseng has demonstrated mild immune boosting activity and is used for many purposes such as prevention and treatment of colds and flus to general stress reduction (Scimone & Scimone, 1998).

In the US, ginseng is considered a nutraceutical. The root is sold directly as a herbal remedy, or it may be extracted or powdered for use in dietary supplements. Ginseng also finds its way into foods, cosmetics, and beverages. The major share of the nutraceutical market comprises products sold as dietary or nutritional supplements in health food stores, pharmacies, supermarkets, and mail order houses. Most ginseng products are covered under the Dietary Supplement Health and Education Act of 1994, and their content is not regulated.

In Europe, ginseng is more closely regulated. Currently, the German government's Commission E allows *Panax ginseng* products containing at least 1.5 percent ginsenosides, calculated as ginsenoside Rg_1, to be labeled for use as a tonic for invigoration and fortification during times of fatigue and debility; for declining work capacity and concentration, as well as during convalescence (Blumenthal *et al.*, 1996).

Ginseng is also specified in the Swiss, Austrian, and French pharmacopeias. The Swiss pharmacopeia requires a total ginsenoside content, calculated as ginsenoside Rg_1, of not less than 2.0 percent. A draft for the European pharmacopeia requires the content of ginsenosides Rg_1 and Rb_1 to be not less than 0.3 percent, measured with an HPLC method (Sticher, 1998).

The global market for herbal remedies is large; in 1997, worldwide retail sales were $16.5 billion. Europe accounted for 45 percent of these sales. The US herbal market was $3.24 billion in 1997, but it is less mature than the European market. The North American market is expected to increase between 50 and 100 percent in 1998 and 1999 and between 20 and 25 percent in 2000 and 2001. Mark Blumenthal, executive director of the American

Botanical Council, estimates the total 1998 US herbal market will be about $4 billion based on a modest estimate of 20 percent growth from 1997 levels. Robert McCaleb, president of the Herb Research Foundation, provided somewhat smaller estimates of the size of the US herbal supplement market, somewhere between $1.6 and $3 billion. He noted that larger estimates may include the reselling of herbal supplements. Decision Resources provided the lowest estimate of the US herbal/plant products market, 1996 sales of $1.6 billion with growth of 7 to 10 percent a year (Scimone & Scimone, 1998).

In 1997, ginkgo, ginseng, and garlic held over 50 percent of sales in the US herbal remedy market. In 1997, US sales of ginseng were $86 million. These figures reflect sales from mass market, food, and drug stores only. Similar figures for ginseng sales in natural product stores were not available, but sales of all herbal formulas in natural product stores were $154 million for the 12-month period ending April 1998, up 25.1 percent from the previous year (Scimone & Scimone, 1998).

Nutraceutical containing foods were rated as a $4 billion industry with growth between 5 and 8 percent a year; specific figures for ginseng sales in this market segment were not available (Scimone & Scimone, 1998). However, the market for phytochemicals as food additives appears to be relatively small. In 1996, the US phytochemical food additives market was estimated at $21 million out of a total $4.8 billion market for nutritional additives (Scimone, 1997).

In 1995, ginseng (*Panax* species) was the fourth highest selling herbal medicine in the US, claiming a 5.9 percent market share (Rawls, 1996). In 1996, ginseng was number three in the herbal supplement market with a 6.4 percent market share (Anon., 1997).

Some nutraceutical products containing ginseng are listed in Table 4. By far the most popular ginseng supplement is Ginsana™. Launched in 1982, sales of Ginsana™ rose 11

percent in 1996 to $40.25 million, controlling 50 percent of the ginseng market (Wilke, 1997).

Table 4. Some Ginseng Products for the Consumer Market

Product Name	Company	Description
CNI milk tea	Ida Lengson	Ginseng extract and Kenyan tea leaves
Energy Sports Drink	Body Systems	Fruit beverage containing ginseng, ginkgo biloba, ginger, kelp, oat seed, protein, and potassium
Ginsana	Boehringer Ingelheim Pharmaceuticals, Inc.	Capsules of standardized ginseng extract G115
Ginseng coffee	Ida Lengson	*Panax ginseng* extract and Columbian coffee
Ginseng mint aftershave	Aubrey Organics	Aftershave contains witch hazel, aloe vera, water, glycerin, ginseng extract, *p*-aminobenzoic acid, cedarwood extract, Siberian pine extract, menthol, citrus seed extract, and vitamins A, C, and E
Ginseng Stamina and Endurance	Naturade	Capsules; white Korean, red Manchurian, and Siberian ginsengs and other herb powders
Pegasus Ginseng - Cardio Guard Formula	BioTek Nutritionals, Inc.	Capsules; 100 mg ginsenosides
Vitabolic Deep Radience Booster	Lancome	Skin cream containing ginko biloba, ginseng, and vitamin C
Willie's Root Zing Root Beer	Willie's Root Zing Sodas	Soda containing root beer and ginseng

Sources: Joyce, 1997; Aubrey Organics, 1998; BioTek, 1998; Boehringer Ingelheim Pharmaceuticals, Inc., 1998a, b; Butcher, 1998; Lengson, 1998; Morrison, 1998; Naturade, 1998

Human Exposure: There is a potential for widespread exposure to ginseng because of its use as a herbal remedy, its presence in dietary supplements and cosmetics, and its use as a food additive. Before the recent boom in the herbal supplement industry, an estimated five to six million people in the US were using ginseng regularly (Chandler, 1988).

A potential for occupational exposure to ginseng exists, especially in the bulk packaging and processing of dietary supplements containing ginseng extracts, powders, and concentrates. Exposure to ginseng from agricultural practices would be expected to be minimal since only the plants and plant roots are handled. No listing was found for ginseng or ginsenosides in the National Occupational Exposure Survey (NOES), which

was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983 (NLM, 1998a).

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace maximum allowable levels of ginseng. Ginseng was not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a Threshold Limit Value (TLV) or Biological Exposure Index (BEI) are made.

International trade in American ginseng is regulated under the provisions of the Convention on International Trade in Endangered Species (CITES), which regulates trade through permit requirements for imports, exports, and re-exports of listed species. American ginseng is listed in CITES Appendix II, controlling and monitoring its trade "in order to avoid utilization incompatible with survival" (Singer, 1979). Harvest and commerce are regulated and restricted both jointly and separately by state agencies, the US Fish and Wildlife Service, and the United States Department of Agriculture (Foster, 1996a).

Since 1994, dietary supplements have been regulated under the Dietary Supplement Health and Education Act (DSHEA). The DSHEA requires no proof of safety for dietary supplements on the market prior to October 15, 1994. Labeling requirements for such supplements allow warnings and dosage recommendations as well as substantiated "structure or function" claims. All claims must prominently note that they have not been evaluated by the FDA, and they must bear the statement "This product is not intended to diagnose, treat, cure, or prevent any disease" (Croom & Walker, 1995).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to ginseng and cancer risks in humans were identified in the available literature.

Characteristic signs and symptoms of overexposure to ginseng have been named ginseng abuse syndrome. These signs and symptoms include morning diarrhea, skin eruptions, sleeplessness, nervousness, and hypertension (Chandler, 1988).

Siegel studied ginseng abuse syndrome in 133 persons using ginseng regularly for at least one month. Some subjects used Siberian ginseng; it was not possible to isolate these cases from those using *Panax ginseng*. Ginseng doses varied from 8 to 10 g three times a day for capsules; 0.5 to 3 g twice a day for roots, 1 to 2 g three times a day for ground powders, and 2.5 to 5 ml a day for extracts. Most subjects experienced CNS excitation and arousal. Fourteen subjects who ingested *Panax ginseng* roots experienced hypertension, nervousness, sleeplessness, skin eruptions, and morning diarrhea; five had edema. Ten became euphoric, restless, agitated, and insomniac. Ten taking high doses (15 g) felt depersonalization and confusion. The average daily dose of ginseng roots was 3 g for persons experiencing ginseng abuse syndrome. One user reported that abrupt withdrawal precipitated hypotension, weakness, and tremor. Ginseng abuse syndrome appeared periodically in the first 12 months of ginseng use but was rarely reported in followup examinations at 18 and 24 months. Taken together, these effects mimicked those of corticosteroid poisoning, strongly suggesting a steroidal mechanism of action (Siegel, 1979).

Ginseng has also caused estrogenic effects in women. These effects included mastalgia with diffuse mammary nodularity and vaginal bleeding in postmenopausal women (Chandler, 1988). In one case study, a 44-year old woman using ginseng face cream developed an episode of postmenopausal bleeding. Her follicular stimulating hormone (FSH) level was 36 mIU; one month after she stopped using the face cream, her FSH level increased to 70 mIU. She began using a measured amount of face cream, her FSH level

decreased, and she had another bleeding episode. An endometrial biopsy specimen showed a disordered proliferative pattern, and she stopped using the ginseng cream. One year later, she had not experienced any further bleeding (Hopkins *et al.*, 1988).

In another case study, a 39-year old man developed hypertension, dizziness, and inability to concentrate during long-term ingestion of ginseng. He stopped taking ginseng, became normotensive within five days, and remained normotensive without treatment; after three months his symptoms resolved (Hammond & Whitworth, 1981).

A 28-year old woman developed a severe headache after ingesting a large quantity of ethanol-extracted ginseng. Cerebral angiograms showed a "beading" appearance in the anterior and posterior cerebral and superior cerebellar arteries, consistent with cerebral arteritis (Ryu & Chien, 1995).

The FDA's Special Nutritionals Adverse Event Monitoring System reported 114 illnesses or injuries associated with the use of special nutritional products and dietary supplements containing ginseng as of May 14, 1998. Thirteen deaths were reported. The following effects were reported for 17 products apparently containing only ginseng as an active ingredient: tonic-clonic seizure and two mild strokes; pruritus and jaundice; vomiting, nausea, diarrhea, and perspiration; dermatomyositis; coma; stomach pains; rash and searing pain; heart palpitations, sweating, and "felt like speeding"; scratched esophagus; nausea, vomiting, dizziness, and blurred vision; atrial fibrillation; fatigue and abnormal LFT's; death; shortness of breath, acute respiratory failure, renal failure, leukopenia and thrombocytopenia, necrotic tissue in bone marrow, followed by death; chest pain, feeling of constriction, heart pounding, anxious, and pale; headache, nausea, and vomiting; and abnormal uterine bleeding (FDA, 1998). No mention of possible preexisting conditions was made.

Ginseng may possibly interact with phenelzine resulting in irritability, tension, and headaches. Its stimulant effects may be additive with other drugs that cause CNS

excitation. Hypertensive individuals who chronically ingest ginseng may have problems with control of blood pressure (Generali, 1988).

Animal Data: *Acute Studies.* The acute toxicity values listed in the Registry of Toxic Effects of Chemical Substances (RTECS) for various ginseng products are shown in Table 5 (NLM, 1998).

Table 5. Acute toxicity data for ginseng

Compound	Route	Species	LD_{50} (mg/kg)
Panax ginseng	oral	rat	750
	oral	mouse	200
	intraperitoneal	mouse	54
Ginseng root extract	intraperitoneal	mouse	545
Ginsenoside No. 3	intraperitoneal	mouse	910
Ginseng, saponin extract	intraperitoneal	mouse	637
Panabolide (TRIS-buffer extract of *Panax ginseng*)	oral	rat	>12,000
	intraperitoneal	rat	550
	oral	mouse	>2,500
	intraperitoneal	mouse	>1,050

Subacute/Subchronic Studies. No evidence of toxicity was observed in groups of four male and four female beagle dogs fed diets containing 0, 1.5, 5, or 15 mg ginseng extract G115 (Ginsana™)/kg body weight/day for 90 days. Although several significant differences in clinical chemical and hematological values were noted, no consistent dose-response relationship occurred and all values were within normal physiological ranges for beagle dogs. Gross and microscopic examinations of major organs revealed no morphological or pathological effects. The highest dose, 15 mg/kg, is approximately twice the recommended dose for humans (Hess *et al.*, 1982).

No toxic effects were noted in rats following ingestion of ginseng extract at daily dose levels of 105-210 mg/kg for 25 weeks (Popov & Goldwag, 1973). No details on this study were available.

Chronic/Carcinogenicity Studies. No conventional 2-year carcinogenicity studies of ginseng or ginsenosides were identified in the available literature.

In a chronic study in LACa mice, no significant differences in mean weights or survival were observed in mice consuming *Panax ginseng* even though increased behavioral responses to mild stress were noted. There were three groups with 90 animals per group. One group consumed ginseng extract from 8 weeks of age throughout life. The second group received ginseng from 52 weeks onward, and the third group served as untreated controls. Ginseng extract was administered in drinking water at a dose of 8 mg/kg/day, corresponding to 40 mg of whole root/kg/day (Bittles *et al.*, 1979). This study was not intended to examine carcinogenicity; histopathology was not performed and no attempt to define maximum tolerated dose was made.

Short-Term Tests: Very little information was found on the potential mutagenic activity of ginseng or ginsenosides. Neither a water extract of three year old *Panax quinquefolius* roots nor an extract containing ginsenosides was mutagenic in *Salmonella typhimurium* strain TM677 with or without metabolic activation (Chang *et al.*, 1986). Dried powders of *Panax japonicum* and *Panax ginseng* dissolved in water (100 mg/ml) were negative in *Bacillus subtilis* strains H17Rec+ and M45Rec- and in *S. typhimurium* strains TA98 and TA100 with or without PCB-induced rat liver S-9 (Morimoto *et al.*, 1981). The root extract of *Panax ginseng* (0-1 μg/ml) produced inhibitory effects on DNA synthesis, measured by thymidine incorporation into V79 Chinese hamster lung cells (Rhee *et al.*, 1990).

An active component of ginseng, ginsenoside Rg_1 stimulated mitosis in the bulb and seedling root tip cells of *Allium cepa;* the most effective concentrations were 0.002-0.006

mg/ml. In contrast, ginsenoside Rb_1 inhibited mitosis in the same cell line; the mitotic indices decreased progressively as the concentrations of Rb_1 increased from 0 to 0.01 mg/ml (Ng & Chao, 1981).

Metabolism: No studies evaluating the metabolism of ginseng or its active ingredients were found in the available literature.

Other Biological Effects: Studies conducted on ginseng and ginsenosides have examined several endpoints, including antitumor, antiviral, and antioxidant effects; effects on the nervous system; effects on the heart, cholesterol, and lipid metabolism; and hypoglycemic activity. According to Foster, inconsistent results have been reported on interpretation of various studies attempting to prove a scientific basis for the activity of ginseng products (Lewis *et al.*, 1983; Lewis, 1986; Foster, 1996b). Shibata and coworkers (1985) noted that many of the inconsistencies can be explained by different procedures used to prepare the ginseng samples, sometimes resulting in extractions lacking biologically active components.

Anticarcinogenic Studies. Korean red ginseng and fresh ginseng root have been evaluated in limited studies for anticarcinogenic activity. In mice, prolonged administration of Korean red ginseng (powder dissolved in water at 1 mg per ml) inhibited or prevented carcinogenesis induced by 7,12-dimethylbenz[a]anthracene (DMBA), urethane, and aflatoxin B_1. Newborn ICR mice were injected with the carcinogen in the subscapular region within 24 hr of birth. They were subsequently administered Korean red ginseng extract in their water from weaning until they were killed. In the group killed at 48 weeks after DMBA treatment, the average diameter of the largest lung adenomas decreased by 23 percent. In the group killed at 28 weeks after urethane treatment, there was a 22 percent decrease ($P<0.05$) in the incidence of lung adenoma. In the group killed 56 weeks after aflatoxin B_1 treatment, there were decreases in the incidence of lung adenoma (29%) and hepatoma (75%) ($P<0.05$) (Yun *et al.*, 1983).

Korean red ginseng administered orally (feed, gavage, drinking water; total dose of 17-25 gm) was reported to inhibit liver cancer induced by diethylnitrosamine (DEN) in Wistar rats. Five animals of the experimental and the control group were killed on the 49th day and the 103rd day after the last of 15 doses of DEN had been administered. The remaining seven animals in the experimental group and six animals in the control group were killed on the 161st day. Rats killed before the 161st day had not developed cancer. On the 161st day, one rat given DEN and ginseng developed liver cancer, but all six rats given DEN without ginseng had liver cancer (Wu & Zhu, 1990).

Korean red ginseng, but not fresh ginseng, also inhibited lung adenoma formation in mice. Newborn NIH(G) mice were given suspensions of four-year-old fresh ginseng root (12.9 mg/ml) or Korean red ginseng extract powder (1 mg/ml) dissolved in drinking water *ad libitum* from date of weaning until they were killed at 9 to 56 weeks. Experimental mice and a positive control group each received a single subscapular injection of urethane, aflatoxin B_1 (AFB), or benzo[a]pyrene (B[a]P) within 24 hours of birth. When red ginseng was given together with urethane, there was a significant reduction in lung adenoma formation observed at 28 weeks (22/30 animals [73%] with adenomas vs. 32/34 [94%]). When red ginseng was given together with AFB, there was also some evidence of a possible chemopreventive effect at 56 weeks (5/29 animals [17%] with adenomas vs. 9/38 [24%]). When red ginseng was given together with B[a]P, a significant anticancer effect was seen (22/80 animals [28%] with adenomas vs. 37/79 [47%]); fresh ginseng was without effect (33/78 animals [42%] with adenomas) (Yun, 1991).

The results of tests for antimutagenic activity of ginseng are limited and somewhat contradictory. Oriental ginseng root, extracted in boiling water, did not demonstrate antimutagenic activity or cytotoxicity in *S. typhimurium* strains TA98 and TA100; the mutagen was BAP and S-9 was prepared from PCB-induced rats. However, an extract of *Panax ginseng* increased the rate of DNA excision repair synthesis in V79 cells treated with UV radiation or methyl methanesulfonate. The extract also decreased mutation frequency at the hypoxanthine-guanine phosphoribosyl transferase locus as measured by

resistance to 6-thioguanine in V79 cells exposed to methyl methanesulfonate. Components of the ginseng extract also exerted an inhibitory effect on the transformation of NIH 3T3 cells initiated by 3-methylcholanthrene, methyl methanesulfonate, and 1-methyl-3-nitro-1-nitrosoguanidine (Sakai *et al.*, 1988; Rhee *et al.*, 1990).

Studies by Tode and coworkers (1993) on ginsenoside Rh_2 provide some basis for the tumor inhibition observed for red ginseng. These authors noted that Rh_2 caused growth inhibition of cultured B16 melanoma cells and inhibition of the proliferation of cultured human ovarian cancer cells. Extending these studies, the authors demonstrated that intraperitoneal and oral administration of Rh_2 in nude mice caused inhibition of human ovarian cancer cell growth.

Ota and coworkers (1997) summarized other known chemotherapeutic effects of ginsenoside Rh_2 on cancer cells. Crude ginsenosides induced phenotypic reverse transformation in cultured Morris hepatoma cells. Purified ginsenoside Rh_2 inhibited the cell cycle progression at G_1 and/or S phases, stimulated melanogenesis, and induced the expression of an untransformed phenotype in B16 melanoma cells. Rh_2 suppressed the formation of sister chromatid exchanges in human blood lymphocytes. The ginsenosides mixture also enhanced the activity of DNA polymerase δ *in vitro*. These findings suggested to the authors that Rh_2 and related ginsenosides possibly modulate the cellular machinery for the cell cycle progression and/or the cell cycle checkpoint control. To elucidate the molecular mechanisms of the actions by Rh_2, the authors focused on cyclin-dependent kinase-2 (Cdk2), a key kinase in the cell cycle progression during the G_1 and S phases. The data clearly revealed that Rh_2 had an inhibitory effect on Cdk2 activity in G_1 arrested cells, but had no inhibitory effect in S arrested cells (Ota *et al.*, 1997).

Other studies indicate that additional ginsenosides may have anticarcinogenic activity. Lee and coworkers (1996) found that Rh_1, as well as Rh_2, was effective at causing differentiation of F9 teratocarcinoma stem cells. Ohtsuka and coworkers (1995) observed

that Rb_1 decreased the activity of the direct acting mutagen 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide in *S. typhimurium* TA100.

CNS Effects. The CNS effects of ginseng are particularly evident when the resistance of the organism is diminished or taxed with extra demands. Thus, ginseng was more effective than placebo in enhancing running performance of young adults, and after taking ginseng radio operators made fewer transmission errors. Experiments with animals also demonstrated the CNS effects of ginseng. For example, rats treated orally with 20 mg ginseng root extract G115 (Ginsana™)/ kg for 3 days showed improved performance in behavioral tests designed to assess memory enhancement and retention. Serotonergic transmission or dopaminergic mechanisms have been implicated in ginseng's effects on behavior (Brekhman & Dardymov, 1969; Petkov, 1978; Kim *et al.*, 1992; Gillis, 1997).

Antiviral Effects. A total of 227 volunteers received a 100 mg capsule of Ginsana™ or placebo for 12 weeks. At week 4, they received an anti-influenza vaccination. By week 12, 42 of the 113 persons in the placebo group and 15 of the 114 persons in the Ginsana™ group developed influenza or common cold, a highly significant difference ($P<0.001$). Antibody titers and natural killer activity levels were significantly higher in the Ginsana™ group by week 8 (Scaglione *et al.*, 1996). Recent studies in normal and athymic rats with pneumonia also showed that animals receiving ginseng treatment for two weeks after infection had significantly reduced bacterial load and less severe lung pathology (Song, 1997).

Diabetes. Administration of ginsenoside-Rb_2 to streptozotocin-induced diabetic rats reduced the level of blood glucose, producing an improvement in hyperglycemia. Rb_2-treated animals also showed a significant decrease in activity of glucose-6-phosphatase, a significant rise of glucokinase activity in the liver, and a moderate increase in glycogen content. Additional studies demonstrated that administration of Rb_2 to diabetic rats stimulated the lipolytic activity of lipoprotein lipase, with a concomitant decrease in the level of triglyceride and very low density lipoprotein in the serum. There was a significant

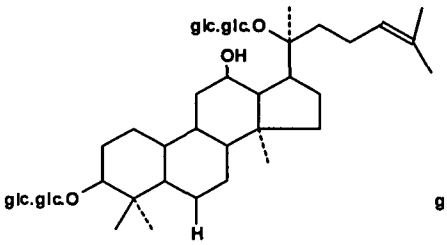
accumulation of lipid in adipose tissue. These data, taken overall, suggested to the authors that ginsenoside Rb_2 may play a role in facilitating the re-esterification of triglyceride fatty acid and glucose in the adipose tissue (Yokozawa *et al.*, 1985).

Cardiovascular Effects. The cardiovascular effects of ginseng root and individual ginsenosides have been studied. Many reports describe vasodilator actions, in some cases followed by vasoconstriction and increase in blood pressure (Gillis, 1997).

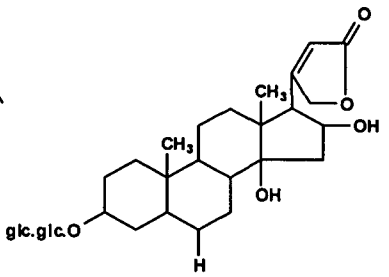
Panax notoginseng extracts, injected iv at concentrations ≥ 0.5 g/kg, produced marked hypotensive response with bradycardia in albino rats. The hypotensive effect was blocked or reversed by pretreatment with atropine, propanolol, and a combination of chlorpheniramine and cimetidine. Similar results were also observed in rabbits. These results were consistent with the use of *Panax notoginseng* as an antiangina and antistasis agent in traditional Chinese medicine (Lei & Chiou, 1986).

Structure-Activity Relationships: No information adequate to judge the carcinogenic potential of ginseng was found in the available literature. Limited information on mutagenicity suggests that ginseng is not genotoxic. Limited information suggests that Korean red ginseng may have anticarcinogenic properties. A much more substantial mechanistic database suggests that some component(s) of ginseng may prove anticarcinogenic. The available information on all nonubiquitous components of ginseng is presented in Appendix 1 as well as throughout the text of this summary sheet.

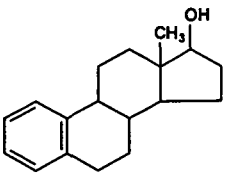
Whether or not the information suggesting anticarcinogenic activity has practical applications depends on the toxicity of ginseng and ginsenosides. Since ginseng is a complex botanical containing possibly hundreds of ingredients, it is difficult to judge its toxicity. This task is complicated by uncertainty about the actual product being administered in many cases. Some concerns must be raised, however, which are suggested by the dammarane structure of ginsenosides. Ginsenosides possess a steroidal backbone



Rb1 Ginsenoside



Digitalin



Estradiol

reminiscent of hormones and of cardiac glycosides. Digitoxin, in particular, bears a close resemblance to ginsenoside Rh_1. While digitoxin has been shown to suppress the growth of breast cancer cells in culture (Kimijima *et al.*, 1992) and inhibit skin tumors induced by DMBA (NLM, 1998b), the utility of cardiac glycosides as chemotherapeutic agents is limited by cardiotonic effects produced.

American ginseng induced the expression of the estrogen regulated genes. Rb_1 ginsenoside was shown to be responsible for induction of estrogen-related genes in the estrogen receptor (ER) positive breast cancer cell line MCF-7. The expression of pS2 induced by ginseng and Rb_1 was inhibited by tamoxifen (Taback *et al.*, 1996). These results support the suggestive evidence of a steroidal effect for ginseng seen in some human case studies. Further studies of ginseng and Rb_1 ginsenoside to determine if the steroidal effects are linked to increased cancer risk seem clearly warranted.

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Appendix 1. Chemicals and their Biological Activities in *Panax Ginseng* Root

The following information on *Panax ginseng* root is contained in the Phytochemical Database, USDA Agricultural Research Service website. The database is maintained by James A. Duke and Stephen M. Beckstrom-Sternberg. It contains an extensive summary of nonubiquitous chemicals identified in *Panax ginseng*, concentrations in parts per million, and a brief summary of health/toxicity data that is available. Similar information is available for American ginseng (Duke & Beckstrom-Sternberg, 1998).

Chemicals	Concentration (ppm)	Health Effects
2-glucoginsenoside-RF	50	no activity reported
α-maltosyl-β-*d*-fructofuranoside		no activity reported
β-elemene		anticancer (cervix)
β-sitosterol-3-o-β-*d*-glucoside		no activity reported
biotin	0.9	antialopecic, antidermatitic, antiseborrheic
campesterol-6'-linolenylglucoside		no activity reported
campesterol-6'-linolylglucoside		no activity reported
campesterol-6'-oleylglucoside		no activity reported
campesterol-6'-palmitylglucoside		no activity reported
campesterol-6'-stearylglucoside		no activity reported
carbon disulfide	1500	no activity reported
d-fructose		no activity reported
d-glucose		no activity reported
disaccharides	33000	no activity reported
fumaric acid		acidulant, antidermatitic, antihepatocarcinogenic, antioxidant, antipsoriac, antitumor
ginsenoside-R_0		antiaggregant, antiedemic, antiinflammatory, fibrinolytic
ginsenoside-Ra_2		no activity reported

Chemicals	Concentration (ppm)	Health Effects
ginsenoside-Rb_1	5000	antiamnesic, antipsychotic, antistress, antitumor, antiulcer, calcium antagonist, CNS sedative, corticosteroidogenic, hypothermic, neurogenic, tranquilizer, vasodilator
ginsenoside-Rb_2	2000	corticosteroidogenic, hypocholesterolemic, hypoglycemic, hypotriglyceridemic, lipolytic, proteinogenic
ginsenoside-Rb_3	50	no activity reported
ginsenoside-Rc	3000	corticosteroidogenic, lipogenic, vasodilator
ginsenoside-Rd	2000	corticosteroidogenic, neurogenic
ginsenoside-Re	2000	calcium antagonist, corticosteroidogenic, vasodilator
ginsenoside-Rf		antitumor
ginsenoside-Rg_1	2000	antiaggregant, antifatigue, antistress, antitumor, aphrodasiac, calcium antagonist, CNS stimulant, homeostatic, hypoglycemic, stimulant, vasodilator
ginsenoside-Rg_2		antiaggregant
ginsenoside-Rh_1		hepatoprotectant
heptadeca-1-en-4,6-diyn-3,9-diol	150	no activity reported
maleic acid		no activity reported
malic acid		bacteristat, hemopoietic, possible laxative, pesticide, sialogogue
maltose		no activity reported
monosaccharides	15000	no activity reported
o-α-*d*-glucopyranosyl fructofuranoside		no activity reported
o-α-*d*-glucopyranosyl glucopyranose		no activity reported
oleanolic acid		abortifacient, anticariogenic, antifertility, antihepatotoxic, antiinflammatory, antioxidant, antisarcomic, cancer preventive, cardiotonic, diuretic, hepatoprotectiue, uterotonic
panacene		cerebrotonic
panaxic acid		cardiotonic, hypocholesterolemic, tonic, vasotonic

Chemicals	Concentration (ppm)	Health Effects
panaxin		cardiotonic, cerebrotonic, CNS stimulant, endocrine-tonic, myostimulant
panaxydol		cytotoxic
panaxynol		antiaggregant, cytotoxic, fibrinolytic
sitosterol-6'-linolenylglucoside		no activity reported
sitosterol-6'-linolylglucoside		no activity reported
sitosterol-6'-oleylglucoside		no activity reported
sitosterol-6'-palmitylglucoside		no activity reported
sitosterol-6'-stearylglucoside		no activity reported
stigmasterol-6'-linolenylglucoside		no activity reported
stigmasterol-6'-linolylglucoside		no activity reported
stigmasterol-6'-palmitylglucoside		no activity reported
stigmasterol-6'-stearylglucoside		no activity reported