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Panax ginseng: A Role in Cancer Therapy?

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Panax ginseng **is a plant that has been used in traditional medicine in China for thousands of years. It is used as a general tonic or adaptogen with chronically ill patients and is frequently featured in traditional medicine prescriptions from China, Japan, and Korea used by cancer patients. The putative active compounds are the ginsenosides, of which there are more than two dozen. These compounds are found in both *Panax ginseng* and in other *Panax* species that are used in herbal medicine. Analysis of ginsenosides is being used in developing quality control assessments for ginseng, which has frequently been adulterated due to its high cost; many currently available standardized extracts do appear to contain the amounts of ginsenosides listed on package labeling. The toxicity of ginseng appears to be low: some of the reports of toxic episodes of ginseng may actually pertain to other components of multicomponent preparations. Very low incidence of toxicity has been observed in ginseng clinical trials using well-characterized preparations. Numerous pharmacological activities of ginseng and the ginsenosides have been explored: the authors review here the activities relating to cancer. Immune system modulation, antistress activities, and antihyperglycemic activities are among the most notable features of ginseng noted in laboratory and clinical analyses. Much testing has been done in humans to explore ginseng's purported antifatigue properties, but this area remains controversial. A number of investigations point to antitumor properties and other pharmacological activities related to cancer, but no trials have yet confirmed a clinically significant anticancer activity. Cancer patients may empirically find ginseng to be useful when they are fatigued, although clinical trials should be conducted to confirm its benefits.**

Keywords: ginseng; Panax; review fatigue; cancer

Introduction

The root of *Panax ginseng* C.A. Meyer (Araliaceae), commonly known as ginseng, has been used in Asia, especially China and Korea, for more than 5000 years, owing to the belief that it is a tonic and panacea that can promote longevity. Its efficacy was first documented in "Sheng-Nung-Pen-Tsao-Ching," an herbal compendium published in the fifth century AD, which states,

> Ginseng tastes sweet, and its property is slightly cooling. It grows in the gorges of the mountains. It is used for repairing the five viscera, quieting the spirit, curbing the emotion, stopping agitation, removing noxious influence, brightening the eyes, enlightening the mind, and increasing the wisdom. Continuous use leads one to longevity with light weight.[1,2]

The plant is indigenous to Korea, northeastern China, and far eastern Siberia. The wild plant is nearly extinct due both to excessive collection from the wild for medicinal purposes and to destruction of its native habitat,[3] mixed coniferous broad-leafed forests of the Manchurian type. Ginseng grows normally exclusively under shade. Relict populations are now found in the Primorsky area of the Russian Federation and the Chinese provinces of Tsilin and Heyludsian. Ginseng is now cultivated in Korea and China. The roots of other species of *Panax*, as well as quite unrelated plant species, have also come to be known as ginseng. Ginseng is of interest to, and used by, cancer patients worldwide. In this article, we concentrate mainly on *P. ginseng*, reviewing its taxonomy, traditional medicine background, phytochemistry, and pharmacology, particularly as they relate to use by cancer patients; we comment on some other types of ginseng as well.

Most research to date has concentrated on Korean or Asian ginseng (*P. ginseng*); in the present review, the term *ginseng* with no other modifier will refer to this species. Early pharmacological studies of ginseng extracts were reported by Brekhman[4] and Petkov.[5] The volume of reports since has become so great that numerous books have been published on the traditional uses, chemical constituents, and biological, pharmacological, and clinical effects of ginseng and its constituents.[6-25] Abstracts and bibliographies on ginseng have also been published.[26] American ginseng, the root of *Panax quinquefolius* L., which grows in

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Table 1. Generally Recognized Species of *Panax*[29]

Panax bipinnatifidus Seem
Panax ginseng C.A. Meyer
Panax japonicus C.A. Meyer
Panax notoginseng (Burkill) F.H. Chen ex C.Y. Wu & K.M. Feng
Panax pseudoginseng Wallich
Panax quinquefolius L.
Panax stipuleanatus H.T. Tsai & K.M. Feng
Panax trifolius L.
Panax vietnamensis Ha & Grushv.
Panax wangianus S.C. Sun
Panax zingiberensis C.Y. Wu & K.M. Feng

North America and has also been the subject of some scientific study, has been an important export commodity to Asian markets since in the 18th century. Originally, American ginseng was collected from its wild habitat in the forests, but due to market demand from the Far East, the cultivation of this plant was started early in the 20th century. It is now grown both in the United States (in Wisconsin) and in Canada (in Ontario and British Columbia).[27]

Botanical Aspects of *Panax*

Panax, the genus to which ginseng belongs, is formed from two Greek words, *pan* (all) and *akos* (cure), based on the reputed use of the plant in China as a panacea.[28] Currently, 11 species are recognized in the genus *Panax* (see Table 1).[29]

Commercially, there are 3 major types of *P. ginseng* preparations. The first is the "fresh ginseng," plants less than 4 years old, which can be consumed fresh. In the production of "white ginseng," derived from plants 4 to 6 years old, the peripheral skin is peeled off the dried root. In the production of "red ginseng," derived from plants at least 6 years old, the root is steamed and dried, resulting in a caramel-like color and resistance to deterioration due to fungi and worms. The latter is particularly valued in China, where it is believed that red ginseng is superior to white ginseng.[30]

In addition to the *Panax* species, other plant species have been given the name of ginseng. The most widely known of these is Siberian ginseng or Russian ginseng. This plant, consisting of the root of *Eleutherococcus senticosus* (Rupr. & Maxim) Maxim. (Araliaceae) has also been used in traditional Chinese medicine for more than 2000 years. It was found to have effects similar to those of *P. ginseng* when Brekhman and his coworkers were looking for a substitute for *P. ginseng*.[31,32] The chemical and pharmacological effects of *E. senticosus* have been reviewed.[33] Other non-*Panax* ginseng species have generally received less research than *E. senticosus*. These are shown in Table 2.[34] These plants do not resemble *Panax* species chemically and should not be considered as members of the ginseng group.

Ethnomedical Aspects

The use of *Panax* species in Chinese medicine and related medical systems as general tonics, which increase vitality in debilitated patients, is the basis of widespread interest in their application in cancer. A full discussion of the traditional medicine uses of ginseng in cancer is beyond the scope of this review. Examples of its use in the treatment of cancer are shown in a compendium of herbal formulas used in cancer by Hsu[35] as well as by other authors. Ginseng, along with *Astragalus membranaceus* Bge. (Leguminosae), is one of the major tonic herbs given in the treatment of cancer in traditional Chinese medicine and is seen as being important in the maintenance of the individual's constitution, often weakened in cancer patients. Formulas containing these herbs may be given as adjuvants to orthodox medical treatment such as surgery, radiation, and chemotherapy or may be used without conventional medical intervention. *Panax* species appear in numerous prescriptions in Hsu's work,[35] including 11 of the most frequently mentioned herbal combinations. These include Ginseng and Ginger Combination, Ginseng and Borax Combination, Ginseng and Ziziphus Combination, and Ginseng Ten Combination.

Formulas that contain *Panax* species are usually composed of multiple herbs and typically include several herbs with tonic effects. For instance, Ginseng and Tang-kuei Ten Combination, a combination consisting of 10 tonic herbs, may be given in cases in which surgery is contraindicated and the patient has severe anemia and a weak constitution. Ginseng and Longan Combination is reported as suitable for those with continuous hemorrhaging and severe anemia who cannot tolerate the former prescription. Many indications for formulas that include ginseng mention such symptoms as weak constitution, low vitality, lassitude, and fatigue. A case study of an elderly lung cancer patient treated in Japan with a formula of 12 Chinese herbs including ginseng and other tonic herbs (the Ninjin Yoei To formula; the Chinese name of the same formula is Ren Shen Yang Rong Tang) was recently reported.[36] After 7 weeks of receiving the formula, the patient's cough disappeared, her appetite recovered, and tumor marker levels (CEA and CA 19-9) were reduced. Traditional medicine assessments also improved.

Table 2. "Ginseng" Species in Commerce That Are Not in the Genus *Panax* [34]

Latin Binomial and Plant Family	*Common Name*
Adenophora polymorpha Ledeb. (Campanulaceae)	False ginseng
Angelica sinensis Diels (Apiaceae)	Women's ginseng
Codonopsis pilosula Nannf. (Campanulaceae)	Poor man's ginseng, false ginseng
Caulophyllum thalictroides Michx. (Berberidaceae)	Blue ginseng
Eleutherococcus senticosus Maxim. (Araliaceae)	Russian or Siberian ginseng
Lepidium meyenii Walp. (Polygonaceae)	Andean ginseng
Pfaffia paniculata Kuntze (Amaranthaceae)	Brazilian ginseng
Pseudostellaria heterophylla Pax (Caryophyllaceae)	Prince's ginseng
Rumex hymenosepalus Torr. (Polygonaceae)	Wild red American ginseng
Withania somnifera Dunal (Solanaceae)	Indian ginseng

Phytochemical Constituents of *Panax* Species

Phytochemical studies on *Panax* species commenced in 1854 when panaquinone was isolated from *Panax quinquefolius*.[37] Since the beginning of this century, a number of Japanese, European, and Korean chemists have been engaged in chemical studies of saponins from *Panax*.[38-42] The most prominent of the phytochemicals isolated from the various species of *Panax* are the saponin glycosides. Many other classes of compounds have been found as well.

Saponins of Panax ginseng

The first 6 saponin glycosides isolated from *P. ginseng* were given the names of panaxoside A, B, C, D, E, and F.[43] More than 60 ginsenosides have subsequently been isolated from various *Panax* species. Based on the triterpene aglycones, the ginsenosides have been classified into 3 major categories, namely, the panaxidiols, panaxatriols, and the oleanolic acid derivatives. A basic summary of the ginsenosides in each category for *P. ginseng*, and the plant parts from which they were isolated, is shown in Table 3. Although this table does not attempt to present a comprehensive or quantitative analysis of all ginsenosides, it does indicate the diverse and complex nature of the array of saponin glycosides in this species, many of which are biologically active.

The relative abundance of each ginsenoside in various *Panax* species has been summarized.[54,55] An early attempt was made to evaluate ginseng quality by measuring panaxadiol and panaxatriol ratios.[8] It was reported that the main root of *P. ginseng* has equal amounts of panaxadiol and panaxatriol saponins, while the panaxadiol/panaxatriol ratio is about 1.5 in the rootlets (smaller roots that branch off the main root). Red ginseng was found to have major ginsenosides similar to those found in white ginseng. However, the less stable malonyl-ginsenoside esters are absent from red ginseng due to decomposition during the steaming process. On the other hand, minor ginsenosides such as 20(R)-ginsenoside Rg_2, 20(S)-ginsenoside Rg_3, 20(R)-ginsenoside Rh_1, and ginsenoside Rh_2 are characteristically found only in red ginseng and are considered degradation products formed during steaming.[56,57] Later efforts in quality control, discussed below, emphasize quantitative measures of ginsenosides, individually or in classes.

Other Constituents Isolated From P. ginseng

Other chemical constituents isolated from *P. ginseng* include alkanes, alkynes, sterols, fatty acids, fatty acid esters (lipids), monoterpenes, sesquiterpenes, phenylpropanoids, chromones, carbohydrates (sugars and polysaccharides), amines, flavonoids, organic acids, and vitamins. Amino acids, nucleic acids, various enzymes, and inorganic compounds (including germanium) have also been isolated from ginseng.

Quality Control

P. ginseng is a popular herb throughout Asia, in Europe, and in North America.[58] However, its high prices make adulteration with less expensive plant material tempting. Numerous attempts to characterize the quality of commercial ginseng preparations have been published. Cui, in 1995, assayed 14 pure *P. ginseng* root preparations purchased in Europe, Argentina, Canada, China, and the United States, as well as 20 *P. ginseng* extracts.[59] Both the total saponin concentrations and the ratios of panaxatriol, panaxadiol, and oleanoic acid saponins were analyzed by high-performance liquid chromatography (HPLC). The total percentage of ginsenosides (weight/weight) varied from 1.9% to 8.1% in the ginseng root preparations and from 4.9% to 13.3% in the extracts. Ratios of panaxatriol/panaxadiol saponins also varied among samples. Among the root preparations, the ratio ranged from 0.30 to 0.62, while in 7 extracts for which individual data were shown, the ratios ranged from 0.30 to 0.40. Thus, not only did the concentrations of saponins in different samples vary, but the ginsenoside composition was also inconsistent among products. Such differences might lead to differences in both clinical and experimental results.

Table 3. ***Panax ginseng*** **Saponins**

Compound Class/Name	*Plant Part*	*Reference*
Panaxadiol saponins		
Ginsenoside Ra_1	Root[a]	44
Ginsenoside Ra_2	Root[a]	44
Ginsenoside Ra_3	Root[a]	45
Ginsenoside Rb_1	Root	46
	Root[a]	47
	Flower buds	48
	Leaves	48
Ginsenoside Rb_2	Root	46
	Root[a]	47
	Fruits	48
	Flower buds	48
	Leaves	48
Ginsenoside Rb_3	Root	49
	Root[a]	47
Ginsenoside Rc	Root	46
	Root[a]	47
	Fruits	48
	Flower buds	48
	Leaves	48
Ginsenoside Rd	Root	46
	Root[a]	47
	Fruits	48
	Flower buds	50
	Leaves	48
Ginsenoside Rg_3 20(R)	Root[a]	47
Ginsenoside F_2	Leaves	51
Ginsenoside Rs_1	Root[a]	47
Ginsenoside Rs_2	Root[a]	47
Quinquenoside R_1	Root	47
Malonyl-ginsenoside Rb_1	Root	56
Malonyl-ginsenoside Rb_2	Root	56
Malonyl-ginsenoside Rc	Root	56
Malonyl-ginsenoside Rd	Root	56
Ginsenoside Rh_2	Root[a]	56
Panaxatriol saponins		
Ginsenoside Re	Root	52
	Fruits	48
	Root[a]	47
	Flower buds	51
	Leaves	48
Ginsenoside Rf	Root	52
	Root[a]	47
Ginsenoside glc-Rf	Root	49
	Root[a]	47
Ginsenoside Rg_1	Root	53
	Root[a]	47
	Fruits	48
	Leaves	48
Ginsenoside Rg_2	Root	52
Ginsenoside Rh_1	Root	48
Ginsenoside F_1	Leaves	48
Ginsenoside F_3	Flower buds	48
	Leaves	51
Notoginsenoside R_1	Root[a]	47
Oleanolic acid saponins		
Ginsenoside R_0	Root	46
Chikusetsusaponin V	Root[a]	47

a. Red ginseng was analyzed.

Ma and colleagues developed an HPLC method for detection of 8 major ginsenosides as a standard for evaluation of the quality of ginseng products, including *P. ginseng*, *P. quinquefolius*, and *P. notoginseng*.[60] They tested samples grown in Asia and North America. The major data reported in the study were the ratios of amounts of different ginsenosides, using ginsenoside Rb_1 (considered to have tranquilizing effects) as the denominator in comparisons. Ratios differed among species, as might be expected. *P. quinquefolius* had a low ratio of the stimulant ginsenoside Rg_1 to Rb_1 (ratio 0.07 to 1.40 among 35 samples) in comparison to *P. ginseng* (ratio 0.51 to 2.08 in 25 samples). This is consistent with the traditional medicinal attribution of "cool" or calming properties to *P. quinquefolius* and "hot" or stimulating properties to *P. ginseng*. The overlap between the 2 species, however, is obvious and could be responsible for overlap in the clinical effects of herbal preparations from the 2 species.

Among 8 *P. ginseng* samples purchased in the United States, the total ginsenoside concentrations ranged from 0.288% to 3.286% in a study that used HPLC-tandem mass spectrometry as an analytical method.[61] Four of the samples declared ginsenoside contents on package labeling: the analyzed ginsenoside levels ranged from 30.6% of the declared level to 136.8% of the declared level. American ginseng was also analyzed in this study, and Rg_1 to Rb_1 ratios were reported. In the 3 *P. quinquefolius* samples in the study, the ratios were all substantially below those of the *P. ginseng* samples, consistent with the previous work by Ma and colleagues.

Continuing concerns about quality control in products in the United States led the American Botanical Council of Austin, Texas, to begin a Ginseng Evaluation Program (GEP) in 1993. The GEP analyzed ginsenosides Rb_1, Rb_2, Rc, Rd, Re, and Rg_1, which together make up 90% of the saponin content of ginseng root and are the putative active compounds of the species. Ginsenoside Rf was also analyzed: this compound is present in *P. ginseng* but not *P. quinquefolius* and was used as a species recognition marker.

The initial report of the GEP presented data on *P. ginseng* products sold in the North American market that claim to be *standardized*, a term that implies to consumers that definite amounts of active compound are contained in the herbal extract.[62] The GEP found substantial variation in the terminology of standardization. For instance, a product could be standardized to deliver 100 mg of ginseng extract per unit (eg, capsule, tablet, softgel) with no claim as to the ginsenoside content of the extract. A product could deliver 100 mg of standardized ginseng extract per unit, again with no claim as to the ginsenoside content

of the extract. The product could, finally, be standardized to contain a minimum of a certain percentage of ginsenosides, usually 4% to 7%. The last terminology is the clearest in specifying the amounts of active compounds to be expected, but products with other terms are found in the market.

The GEP analyzed multiple lots of 13 standardized ginseng products to determine the extent to which they met label claims of standardization as to percent ginsenosides, or the standard of 4% ginsenosides if no claim of ginsenoside content was made on the product label (ie, the first 2 types of standardized products listed above).[62] Of the 8 products that made specific claims, 4 contained the claimed levels of ginsenosides in 80% to 100% of the lots analyzed. In 1 product, fewer than 40% of the lots contained the claimed levels of ginsenosides. For those products that did not make specific claims of ginsenoside contents, 4 of 5 met the standard of 4% total ginsenoside content in all lots tested. The majority of standardized ginseng products did thus meet minimal standards of quality control. However, the GEP recommended revisions of product labeling to clarify the ginsenoside dose that could be expected per unit so that consumers have a clearer idea of ginsenoside dosages they may expect from the products they purchase (recommended ginsenoside daily dosages range from 6 to 180 mg, depending on the source).

Toxicity Assessment

The root of *P. ginseng* was nontoxic to rats,[63] dogs,[64] and humans[65,66] on oral ingestion. A 95% ethanol extract was nontoxic by either the oral or the intraperitoneal (ip) routes in rats.[67] The aqueous extract produced generalized toxicity in mice at the ip dose of 0.5 g/kg/day/7 days[68] but was orally nontoxic in the same animal species at various doses.[69,70] The LD_{50} values of the total saponin fraction in mice were 0.695 and 1.49 g/kg, respectively, for the ip[71] and subcutaneous (sc)[72] routes. Oral administration of the saponin fraction to beagle dogs showed it to be nontoxic at 15 mg/kg[73]; it was nonembryotoxic at doses of 1.5, 5.0, and 15 mg/kg.[74] The fraction potentiated insulin shock in mice.[75]

The relatively nontoxic nature of the root extracts was further supported by the antitoxic actions of both the aqueous extract and saponin fractions. Aqueous extracts reduce the toxic effects of 5-fluorouracil and mitomycin C in rabbits[76] and protected the fibroblast–fetal lung degeneration by adverse environmental conditions.[77] In addition, the water and methanol extracts were nonmutagenic when tested in the *B. subtilis* H-17, *Salmonella typhimurium* TA 100, and TA 98 systems,[78] and the saponin fraction was nonmutagenic in the *S. typhimurium* TA 100 and TA 98 systems.[79] Polyacetylenes, which have been reported as anticancer components of ginseng, were tested for toxicity in Wistar rats. They induced suppression of body weight growth; however, 4 days after stopping administration of polyacetylenes, the growth rate recovered.[80]

Several reports have suggested possible toxicities of ginseng in humans or possibilities of adverse effects due to misuse or overdose. Some of the reports of adverse events attributed to ginseng, however, are considered to be unreliable due to lack of sound experimental design or proper botanical identification of the substances in question; we therefore mention these issues where appropriate. Siegel[81] coined the term *ginseng abuse syndrome* after studying 133 users of ginseng in an open trial in Los Angeles, Calif. The reported average daily intake was 3 g, but actual consumption varied widely, with some users taking up to 18 g daily. Twenty-two of the subjects experienced symptoms such as hypertension, nervousness, sleeplessness, skin rash or diarrhea, confusion, depression, or depersonalization. Some subjects reduced their dosage. A later study by the same author[82] examined use of American ginseng products and reported similar symptoms among a group of 10 drug addicts. The study was not restricted to a single dosage form; rather, a wide variety of ginseng products were used, including root, capsules, extracts, cosmetic creams, tablet, and teas, and no effort to estimate appropriate dosage was made. In neither study were the chemical contents of the products characterized or controlled. It is now widely recognized that this syndrome is not grounded in clinical, phytochemical, or pharmacological evidence.

Nevertheless, reports of the syndrome continue to surface, with similar methodological deficiencies. Overuse and excessive use of ginseng are claimed to lead to headaches, insomnia, hypertension, and palpitations.[83] A case study described as ginseng abuse recorded a 40-year-old man complaining of heaviness and congestion in the chest, palpitations, and a heartbeat of 90 beats per minute under conditions of no exertion. He had recently attended a convention where he took 5 to 6 cups of coffee (more than his normal amount), vitamins, and a "normal" dose of a combination product including *P. quinquefolius* and *E. senticosus*. Blood pressure was normal, as were heart sounds and electrocardiogram. Symptoms disappeared with discontinuance of the ginseng product.[84] The exact composition of this product has never been validated, however, and the proportion of symptoms attributable to the *Panax* component is in doubt. There are indications from traditional herbal practice that adverse symptoms may be attributable to

improper use of ginseng, although these are naturally not documented scientifically. Ginseng is described by one herbalist as causing feelings of heaviness, aggressiveness, chronic spasmodic pains, and congestion when used inappropriately for long periods. Ginseng would usually be prescribed only in cases in which there is a deficiency of energy or other conditions of depletion (eg, shock, prostration, diarrhea, loss of appetite, dehydration, diabetes, forgetfulness, fatigue, and weakness) and would not be taken during conditions of acute diseases, inflammatory conditions, colds, and infections in traditional practice.[85]

Other reports of untoward effects from ginseng products are also found in the literature. Sonneborn and Hansel[86] summarize several. Reports of reproductive effects from Europe and the United States include evidence of estrogenic effect in a vaginal smear from a 62-year-old woman who took "Rumanian ginseng." This product may actually have been *E. senticosus* (Siberian ginseng) since there is no botanical species known under the common name Rumanian ginseng. Extracts of *E. senticosus* have been reported to have an affinity for estrogen receptors. A 72-year-old woman reported vaginal bleeding after taking a European product containing *P. ginseng*, vitamins, and minerals; controlled trials of this product in Switzerland, however, did not show any effect on testosterone, luteinizing hormone, follicle-stimulating hormone, or estradiol in men or women. A 44-year-old woman reported abnormal uterine bleeding while using a Chinese ginseng cream. A 70-year-old woman developed mastalgia, and 5 women aged 25 to 40 years developed breast symptoms, all while taking ginseng products.

Other case reports of adverse effects attributed to ginseng include manic episodes and hypertension. A recent report describes a manic episode in a woman with an affective disorder who was taking ginseng. Symptoms disappeared with low doses of neuroleptics and benzodiazepines.[87] A case report of a 35-year-old woman with a history of depression noted a manic episode a few days after ginseng ingestion.[88] Hypertension, along with dizziness and inability to concentrate, was reported in a 39-year-old man who had taken unspecified ginseng products for 3 years; the condition disappeared when he stopped taking the products. A report of acute hypertension and pressure headaches in a writer who took ginseng tea for 8 days is also in the literature.[86] However, a slight reduction in diastolic blood pressure was observed in a trial in which 30 subjects were given *P. ginseng* extract for 28 days. A slight increase in the QTc interval was also observed, but neither effect was felt to be of clinical significance. No other changes in electrocardiographic or hemodynamic variables were observed.[89]

Reports of adverse events in ginseng clinical trials include diarrhea observed in 2 of 25 participants in a trial in Australia, although controlled trials with higher doses of ginseng did not observe such effects.[86] A systematic global review by Coon and Ernst[90] of adverse effects of *P. ginseng* in clinical trials reported that the incidence of adverse events in experimental groups taking ginseng was similar to that for placebo groups. The most frequently reported adverse events were headaches, sleep disturbances, and gastrointestinal effects.[90] Gastrointestinal side effects are frequently observed in clinical drug trials under both placebo and experimental conditions, and this report may represent a nonspecific reaction. Coon and Ernst[90] point out that causality of adverse events based on isolated case reports submitted to national drug safety agencies is difficult to determine. They concluded that their review of clinical trial data of ginseng monopreparations indicates that these are rarely associated with adverse effects beyond mild and transient disturbances; multicomponent preparations may be associated with some adverse effects, but the degree to which these are attributable to ginseng is not clear.

Possible herb-drug interactions between ginseng and conventional drugs have been reported. A 27-year-old man developed Stevens-Johnson syndrome after taking larger than usual doses of ginseng; he was also taking aspirin and an unspecified antibiotic.[91] Two women taking phenelzine, an antidepressant, were reported to have reactions that included headaches, insomnia, tremulousness, irritability, and vague hallucinations when they took ginseng products in addition to the phenelzine.[86] A man with membranous glomerulonephritis being treated with furosemide and cyclosporin was hospitalized with edema and hypertension 2 days after taking large doses of a germanium-containing ginseng preparation.[92] Finally, a drug interaction between ginseng and warfarin was reported in a 47-year-old man with a mechanical aortic valve. After 2 weeks of ginseng ingestion, his international normalized ration (INR) was lowered from 3.5 to 1.5. When ginseng was stopped, the INR returned to 3.3 in 2 weeks.[93] A systematic review by Izzo and Ernst[94] noted the interactions with warfarin and phenelzine, as well as a lowering of blood alcohol level. Vaes and Chyka[95] pointed out that the warfarin interaction is based on a single case, making it difficult to evaluate the true risk for interactions. A more scientific assessment of the potential for drug interactions comes from observation of ginseng effects on cytochrome P450 drug-metabolizing enzymes. Standardized *P. ginseng* extract was found to decrease CYP1A1, CYP1A2, and CYP1B1 activity in an in vitro study; high levels (50 μg/ml) of ginsenosides Rb, Rb2, Rc, Rd, and Rf also inhibited the activities of CYP1

enzymes.[96] A human study of ginseng effects on CYP1A2, CYP2E1, CYP2D6, and CYP3A4, however, found no significant effect on these enzymes, which are the predominant enzymes responsible for the metabolism of drugs used in cancer care, such as chemotherapy agents.[97,98]

Ginseng is thus not without potentials for toxicity; however, for most individuals, the risk of adverse reactions is quite low. One of the more commonly reported side effects in clinical practice is insomnia; this can be overcome if ginseng doses are taken in the morning rather than in the evening. Patients taking drugs for which interactions with ginseng have been reported should also be counseled against its use, based on a precautionary principle.

Biological and Pharmacological Actions of *P. ginseng*

Modern biological studies of *P. ginseng* were initiated in the late 1950s with the pioneering work of Brekhman in the USSR and of Petkov in Bulgaria. Interestingly, Brekhman and Dardymov[31,99] started their study using human subjects, with animal experiments being carried out subsequently as confirmatory assays. They found that Soviet soldiers receiving *P. ginseng* ran faster in a 3-km race than did those receiving a placebo and that radio operators taking this drug were found to transmit text faster and with fewer mistakes than did the controls. Brekhman confirmed his results reported in humans with experiments on mice, which were put into water where they swam until they were completely exhausted, taken out of the tank, allowed to rest, and then repeated the swim. The second swim of the mice is usually much shorter. The group receiving the extract of *P. ginseng*, however, swam longer during the second swimming test than did the controls. In other early work, Petkov[4,100] reported that *P. ginseng* has central nervous system–stimulating, hypotensive, respiratory stimulation, blood-sugar-lowering, insulin potentiation, erythrocyte count, and hemoglobin content elevation effects.

Following these reports and the ethnomedical panacea reputation of this plant drug, pharmacological studies on every conceivable activity have been carried out. One of the most significant series of studies were carried out by Takagi and his coworkers,[101] in which *Panax ginseng* root was subjected to a series of blind screening tests to evaluate its pharmacological effects. Their findings and the early findings of others are summarized in Table 4. There appear in Table 4 some apparently contradictory results, which would call into question the validity of these experiments. However, systematic pharmacological studies carried out during each step of the chemical fractionation of *P. ginseng*[102] and on some of the resulting pure isolates (ginsenosides)[103-106] showed that the plant material (root) contains constituents that have opposite pharmacological actions. Thus, depending on the concentration of a specific saponin at the time of harvest, opposite pharmacological actions could be observed.

Table 4. Pharmacological Effects of *P. ginseng* Extracts: Early Assessments

Effect	*Reference*
Central nervous system (CNS) stimulation	31, 98, 108
CNS depressant	108
Cholinergic effect	109
Histamine-like action	110
Hypotensive	111, 114
Hypertensive	112
Papaverine-like action	4
Serotonin-like action	113
Non-antihistamine-like action	4
Antihistamine-like action	111
Hypoglycemic action	114, 115
Antiplatelet action	116

The term *adaptogen* is frequently applied to the therapeutic activity spectrum attributed to ginseng in traditional practice. This term was originally used to describe a substance that increases the nonspecific resistance of an organism to adverse influences.[107] Brekhman and Dardymov[31,98] defined adaptogen as a substance that (1) must be innocuous and cause minimal disorders in the physiological functions of an organism, (2) must have a nonspecific action, and (3) usually has a normalizing action irrespective of the direction of the pathological state. This purported adaptogenic effect of *P. ginseng* appears to be rooted in its immunomodulatory, antioxidant, antistress, antifatigue, and endocrine actions, which may contribute to the "wellness" of the patient. Other potential activities that are of relevance to cancer management include antitumor/cytotoxic, antihyperglycemic, anticoagulant, and hormonal activities. We review here some of the basic pharmacology of *P. ginseng* in these areas. Recent systematic review articles discuss the efficacy of ginseng in improving physical and psychomotor performance in basically healthy subjects. We will not discuss these areas in detail, although we will discuss the findings of the reviews.

Immunomodulatory Effects

In this section, we will concentrate on immunostimulatory effects of ginseng relevant to cancer. Immunostimulation effects, as manifested by positive tests for interferon induction, phagocytosis, natural killer (NK) cells, and B and T cell stimulation in various animal species including the mouse, guinea pig, and human, have been reported for the aqueous,[117]

methanol,[118] ethanol, butanol, and petroleum ether extracts[119]; the saponin fraction[120]; and the polysaccharide fraction.[121] The following immune effects of the saponin fraction have been reported: an increase in NK cytotoxic activity[122] and an increase in the tumoricidal activity against K562 tumor cells by macrophages.[73] Ginseng extract enhanced cell-mediated immune response,[123] and red ginseng extract augmented NK activity in mice.[73] A ginseng polysaccharide extract enhanced the lytic death of L929 cells by murine macrophage, as well as tumoricidal activity against YAC-1 cells. TNFα activation, expression of nitric oxide sythase, and nitric oxide production were all elevated.[124] The extract also increased cytotoxicity of macrophages against B16 melanoma and induced phagocytosis.[125] Administration of 20(S)protopanaxatriol, the main bacterial metabolite of the panaxatriol ginsenosides, reduced growth of implanted B16 melanoma in mice. In vitro studies revealed no effect on tumor cell growth; rather, cytotoxicity of splenic NK cells against the tumor cells was stimulated.[126]

Studies of immunomodulatory effects in humans have also been reported. A double-blind, placebo-controlled multicenter trial in 227 patients given 200 mg standardized ginseng extract daily reported an immune stimulant effect after vaccination against the common cold or influenza. After 12 weeks of treatment, antibody and NK titers were twice as high in the treatment group as in the placebo group, and the frequency of colds and flu decreased further in the treatment group. There were 9 reports of adverse reactions such as insomnia, abdominal discomfort, and anxiety in the treatment group.[127] NK cell activity toward K562 cells and antibody-dependent cellular toxicity toward herpes-infected H-9 cells were improved in blood samples from patients with chronic fatigue or AIDS given ginseng.[128] In a study of 60 healthy volunteers, groups given ginseng aqueous or standardized extract had an increased chemotaxis of polymorphonuclear leukocytes, phagocytic index, and number of T_3 and T_4 lymphocytes. The group given standardized extract also had an increase in activity of NK cells and increased T_4/T_8 ratio.[129]

Antioxidant Effects

Several studies have indicated antioxidant effects for ginseng extracts or compounds. Ginsenosides decreased formation of lipid peroxides after trauma in mice.[130] The saponin fraction showed an anti-ischemic effect in rats,[131] while the root decoction inhibited thio-barbituric acid production in vitro.[132] The ginsenoside fraction and the saponin fraction have shown free radical scavenging activity in endothelial aortic cells and in an in situ lung model.[133,134] Antioxidant effects have also been shown in animal models involving carbon tetrachloride–induced hepatotoxicity[135] and free radical injury to pulmonary epithelium.[136] Smokers (at least 20 cigarettes per day) were given red ginseng or other antioxidants (vitamin E, beta-carotene, vitamin C). Plasma antioxidant nutrients rose, while levels of 8-hydroxydeoxyguanosine (an indicator of oxidatively damaged DNA) and carbonyl content declined in a time-dependent manner in comparison with those given placebo.[137] Malondialdehyde concentration also decreased gradually after 4 weeks of supplementation with the same antioxidants.[138] Antioxidant effects of various ginsenosides were evaluated against the hemolysis of human erythrocytes induced by a water-soluble free radical compound. Different ginsenosides had different levels of antioxidant activity, while some, when tested in combination with other ginsenosides, had pro-oxidant activity.[139]

Antistress Effects

Stress refers to phenomena that expose the body to adverse external influences; these influences may be physical, chemical, or biological. *P. ginseng* extracts have been reported to protect, or help animals and human to recover, from various types of stress.[7,140,141] Some specific effects on various type of stress are as described below.

Physical Stress

High and low temperature. Animal studies are the standard pharmacological assays for temperature stress. A dose of *P. ginseng* extract that did not have any effect on the adrenal ascorbic acid content in normal rats accelerated the restoration of normal adrenal ascorbic acid concentrations after their initial depletion during heat or cold stress.[142] Treatment with root saponins partially prevented the rectal temperature decline in normal rats exposed to cold stress without affecting plasma levels of glucose, lipids, or corticosterone.[143] However, such an effect was not observed in adrenalectomized rats. Ginsenosides Rb_1 and Re were also reported to inhibit the decrease of adrenal ascorbic acid levels during heat stress.[144] Pure ginsenosides, Rb_1, Rb_2, Rc, Re, Rg_1, and 20S and 20R prosapogenins were also found to exhibit antistress effects.[145] Ginsenoside Rb_1 was observed by Wang and Lee[143] to improve thermogenesis and cold tolerance in rats.

Radiation protection. Extracts of *P. ginseng* had radioprotective effects or prolonged the survival time of irradiated mice.[146,147] Radioprotective effects of *P. ginseng* in rats and guinea pigs have also been

reported.[148] An extract of *P. ginseng* accelerated the hematological recovery of mice after x-ray irradiation.[149] Kim et al have reported radioprotective effects of ginseng proteins on γ-ray irradiated ICR mice. Ginseng protein fractions enhanced the recovery of body and splenic weights and increased the amount of DNA in liver significantly, accelerated the normalization of erythrocyte counts,[150] and reduced DNA damage to normal cells (effects of ginseng on tumor cells exposed to radiation are discussed below).[151]

Chemical Stress

Studies of chemical stress in animals may be applicable to the use of ginseng to moderate stress in patients undergoing cancer chemotherapy. Effects of ginseng on chemically induced hepatitis and on protection from effects of cancer chemotherapy drugs have been reported. For instance, an extract of *P. ginseng* decreased damage to rat liver from carbon tetrachloride intoxication[152] and inhibited the elevation of serum glutamic pyruvic transaminase in carbon tetrachloride– or thioacetamide-intoxicated mice.[153,154] Among the studies of ginseng and chemotherapeutic agents, a water extract of ginseng and *Angelica sinensis*, another traditional tonic medicine of China, was found to reverse cisplatin-induced leukopenia in mice.[155] Ginseng saponin fraction reduced cyclophosphamide-induced immune suppression in mice.[156] Anticlastogenic activity was observed in mice treated with ginseng extract and exposed to mitomycin or to cyclophosphamide.[157] Ginseng and Tang-kuei Ten Combination is a commonly used Chinese combination herbal preparation including ginseng, *Astragalus membranaceus*, *Atractylodes macrocephala*, *Polyporus hoelen*, *Angelica sinensis*, *Paeonia lactiflora*, *Cnidium monnieri*, *Cinnamomum zeylanicum*, *Rehmannia glutinosa*, and *Glycyrrhiza uralensis*. A dosage of 50 mg/kg was observed to reduce the lethality and renal toxicity of cisplatin administered at toxic doses to ICR mice, without reducing the antitumor effect of the cisplatin in animals inoculated with Ehrlich ascites tumor. The dosage used was reportedly proportional to that used in clinical treatment of adult patients.[158]

Biological Stress

After being administered *P. ginseng* saponins at a dose of 50 mg/kg iv for 4 days, mice were found to be more resistant to infections by *Staphylococcus aureus*, *Escherichia coli*, and *Salmonella typhi*.[159] Oral administration of *P. ginseng* at 0.1 g/kg/day for 3 weeks, followed by an injection of trypanosomes, reportedly attenuated the process of trypanosomiasis; the life span of the treated mice was prolonged, and the appearance of trypanosomes in their blood was delayed.[160] *P. ginseng* also prevented the development of fever induced by typhoid and paratyphoid vaccines.

Endocrine Effects

Ginseng extract was reported to increase adrenal cAMP in intact rats but not in hypophysectomized rats.[161] The results suggest that it acts on the hypothalamus or pituitary so that the latter secretes adrenocorticotrophic hormone (ACTH), which then stimulates the adrenal cortex.[162] After the ip administration of ginsenosides Rb_1, Rb_2, Rc, Rd, and Re, both ACTH and corticosterone levels are increased in the plasma. Their increase is suppressed by pretreatment with dexamethasone, which acts on the pituitary and hypothalamus.[163] Ginseng components may stimulate or inhibit cAMP production: both the diol saponin and triol saponin may have reciprocal effects on pepsinogen secretion regulatory agents.[164] Gincosan, a combination of *P. ginseng* and *Ginkgo biloba* L. (Ginkgoaceae), increased the serotonin level in all brain structures except for the pons and decreased the noradrenaline level in Wistar rats. It decreased the serum level of prolactin and greatly increased the serum level of ACTH.[165] Ginsenoside Rg_1 was found to bind to the glucocorticoid receptor.[166]

Antifatigue Activities

Following the initial studies of the antifatigue activity of *P. ginseng* on Russian soldiers and on radio operators, antifatigue studies were carried out on laboratory animals. Various parameters have been used to measure this activity, including swimming, running against an endless rope, activity wheels (treadmill exercise), recovery from exhaustion, and oscillation movements. Numerous studies have reported positive results. For instance, the antifatigue effect of a ginseng root preparation has been reported by Rüeckert,[167] and the same effect for red ginseng was reported by Saito and Bao.[168]

Ginsenosides Rg_1 and Rb_1[169,170] have been reported to possess antifatigue activity. The saponin fraction of red ginseng was shown to have an antidepressant effect in mice against desmethylimipramine-induced immobility and was synergistic with various antidepressant drugs; however, the fraction had no effect on immobility induced by forced swimming, another test used to assay antidepressant activity that could also reflect antifatigue activity.[171] However, the entire plant extract did display antidepressant activity in a forced swimming model.[172] Ginseng extract was found to have a behavioral effect that was similar to that of imipramine, but longer lasting, in another experiment using the forced swimming model.[173] The antifatigue activity of *P. ginseng* in mice has also been

compared with that of piracetam, a clinical antistress drug.[174] Ginseng increased endurance in both male and female mice, while piracetam showed an antifatigue effect only on the male mice. Antifatigue activities for the 1-butanol (saponin) fractions of *P. ginseng*, *P. quinquefolius*, and *E. senticosus* (all root preparations) have been reported.[175] Forty-eight hours before and again 1 hour before the swimming test, drugs were administered by stomach intubation. No significant prolongation of swimming time was observed, nor was the plasma lactic acid level affected.

The effects of *P. ginseng* extract on tissue glycogen and adrenal cholesterol depletion during prolonged exercise have been studied.[144] Ginseng extract inhibited by 21% the decrease of adrenal cholesterol found in untreated rats after 3 hours of swimming. It had no effect on hepatic glycogen but did have pronounced inhibitory effects on endogenous glycogen utilization in white skeletal muscle during exercise, indicating that ginseng has carbohydrate-sparing actions during prolonged exercise. In a similar test,[176] the lactic acid, total lipid, and glucose levels in the serum and protein, DNA, RNA, total lipid, and glycogen levels in liver and muscle were measured before and after the forced swimming test. It was found that the glycogen levels in both muscle and liver were higher in rats treated with saponins of stems and leaves of *P. ginseng* (SSLG) than in control rats after the forced exercise. Only when the rats were fatigued did the group receiving SSLG consume fat as an energy source and so spare carbohydrates. The blood total lipid level of the mice receiving SSLG was increased after forced exercise, while the content of total lipid in muscle tissue was lowered. It was inferred that the raising of blood lipid level by SSLG could be one aspect of its antifatigue mechanism. A standardized *P. ginseng* extract (G115, Pharmaton) stimulated D-glucose transport; this can be related to the suggestion that ginseng can alter the mechanism of fuel homeostasis during prolonged exercise.[177]

During the 1980s and 1990s, numerous human trials of ginseng and multicomponent preparations containing ginseng were conducted to determine the effects of ginseng on fatigue and various other aspects of human performance. In the past 10 years, double-blind, placebo-controlled trials became more common as investigators attempted to incorporate principles of good experimental design into their studies. Two recent systematic reviews, by Vogler et al[178] and Bahrke and Morgan,[179] have evaluated these studies. Both reviews located many randomized studies. Both negative and positive findings were reported from these studies in various aspects of human performance: reports of improvements in ability to perform physical or mental work of various types contrast with studies in which no such improvements were found. Further examination of the designs of these studies, however, revealed that important principles of clinical research were skirted in almost all of them. Only half the studies in the review by Vogler et al[178] had a Jadad score of more than 3 on a scale of 5 (the Jadad score rates the quality of research design), indicating a very low quality of research for the entire group of studies. Bahrke and Morgan[179] emphasized the numerous studies performed in the sports context that found no effects of ginseng on performance, pointing out that most of them had sample sizes too small (8 to 10 subjects per group) to provide adequate statistical power to detect reasonable differences.

Recent publications on ginseng have concentrated on quality of life, well-being, and memory enhancement. A randomized trial of ginseng in 83 young adults (mean age = 26 years) used the G115 standardized ginseng extract and measured positive affect, negative affect, and total mood disturbance. No difference in any of these measures of psychological well-being was found.[180] A small, randomized study of 30 adults, using the SF-36 Health Survey, a validated general health questionnaire, found that after 4 weeks of ginseng dosing, the group that received ginseng had higher scores on the social functioning, mental health, and mental component summary subscales of the survey instrument, although overall scores were not significantly different. The subscale differences disappeared after 8 weeks of ginseng intake.[181] Ginseng extract G115 was given to healthy young adults at 3 dosages in a double-blind crossover study of its effect on cognitive performance in acute administration. Improvements in scales of "quality of memory" and "secondary memory" were reported with the 400-mg dosage of ginseng extract. The 200- and 600-mg doses were associated with decrements in "speed of attention." Subjective rates of alertness were lowered after the 2 lower doses.[182] Three studies of the effects of a combination of a standardized extract of ginseng (G115) and a standardized extract of *Ginkgo biloba* L. (Ginkgoaceae) have found positive effects on memory variables. Acute administration of the combination in a double-blind crossover study in 20 young adults resulted in improvement in "quality of memory," owing to an improvement in secondary memory rather than working memory. A decrease in "speed of attention" was also found; both effects are similar to those noted above for the ginseng-only study by the same authors.[183] A trial of similar design with the same combination reported improvements in serial subtraction tests.[184] A 14-week randomized trial in 256 middle-aged volunteers using the combination was found to increase an Index of Memory Quality by an

average of 7.5%, which reflected improvements to both working memory and long-term memory.[185]

Studies on ginseng in elderly patients have also been published. A meta-analysis of 21 studies on *P. ginseng* in the treatment of elderly patients with low vitality was published in 1988.[186] Approximately 1 g of ginseng root daily at breakfast and lunch was the usual dosage in the studies. Studies reported increased concentration, better memory, and faster reaction times after ginseng dosing for 1 month or more; the meta-analysis attributed a major effect to the ginseng supplements and a less effect to placebo. An uncontrolled study of 15 elderly patients with chronic respiratory disease reported improved pulmonary function, oxygenation, and 6-minute walking distance after 3 months of ginseng supplements.[187]

While recent studies of the effects of ginseng or a ginseng/ginkgo combination on memory appear promising, the evaluation of the antifatigue properties of ginseng is still incomplete and clouded by difficulties in experimental design. What were the specific difficulties in studies of ginseng and human performance? Differences in preparations used, a variety of dosing schedules, short periods of ginseng supplementation, no monitoring of compliance with planned dosing schedules, and an almost complete lack of any chemical analyses of products used have complicated the evaluation of human research on ginseng and performance. In addition, investigators used a variety of different measures for performance, not all of which have been validated for the populations they used. Most well-designed published studies used ginseng in combination with other herbal or nutritional substances: while this may be representative of how much of the population takes ginseng, it does not allow evaluation of its effects on human performance. Bahrke and Morgan[179] pointed out that even the best-designed of the trials that they evaluated, which used power calculation to determine adequate sample size and monitored compliance, had many other flaws in design and analysis. The study of fatigue in human subjects is complicated by the varied etiology of feelings of fatigue in humans: depression, subclinical illness of several types, and lack of sleep are among the more common causes, and this is not taken into account in the design of studies. Finally, many of the more recent performance studies on ginseng have used healthy young adults as subjects. In traditional Chinese medicine, ginseng is not prescribed for this population: ginseng is normally used by older adults or convalescents. No studies of the effects of ginseng in fatigued cancer patients were found. Because of the complex etiology of fatigue in cancer patients and the lack of agreement about proper instruments for measurement of fatigue in this population, future studies in this area should be designed with great care.

Antitumor/Cytotoxicity Activities

The antitumor/cytotoxicity profiles of the various extracts and saponins of the *P. ginseng* root are unclear based on conflicting literature reports available. Numerous studies have examined cytotoxicity of ginseng and its fractions and compounds in vitro and in vivo against a wide variety of cancer cell lines or in vivo neoplasms. Different studies have reported no cytotoxic or growth inhibitory activity, or definite activity, as well as weak or questionable activity. The following selection of results is organized by degree of activity and cell line or model system and notes the extract or fraction type, or compound, and reference for each result.

Inactive results for extracts/fractions were reported as follows: Ehrlich ascites cells in vitro or in mice: ether, methanol, water extracts[188]; JTC-26 cells: water[189]; HRT-18 rectal carcinoma: water[190]; Widr colon cancer: ethanol, water, methanol,[191] protein[192]; Hep-2 carcinoma: ethanol, methanol[193]; HS-578-T: ethanol[193]; astrocytes (MTT assay): saponin fraction.[194] Negative and weak results were reported for other extracts on the same cell lines by some of these authors. Results indicating stimulation of cancer growth have also been noted: a ginseng extract induced growth of MCF-7 breast cancer cells, although it did not show activation of estrogen receptors and had no effect on uterine weight when administered to mice.[195]

Active results for extracts/fractions were reported as follows: Ehrlich ascites tumor in mice: ethanol-water[196]; L1210 cells: ether, hexane, ethyl acetate,[197] petroleum ether,[198] saponin fraction[199]; sarcoma-180 cells or in mice: ethyl acetate, hexane,[200] saponin fraction [201]; hepatocarcinoma G-2: petroleum ether[202]; L-929 cells: petroleum ether[203]; leukemia P-388: water[194]; A-549 cells: ethyl acetate[203]; Leuk SNU-717 cells: saponin fraction[203]; DMBA-induced lung carcinoma: saponin fraction[205,206]; benzo(a)pyrene-induced lung carcinoma: saponin fraction.[207] A ginsenoside fraction induced differentiation of leukemia cells derived from clinical samples.[208] The petroleum ether extract inhibited the growth of 3 human renal cell carcinoma lines and was found to block cell cycle progression at the G1-S phase transition.[209] American ginseng extract inhibited growth of MCF-7 (estrogen-sensitive) and MDA-MB-231 (estrogen-insensitive) cell lines; activity was attributed to transcriptional activation of the p21 gene.[210]

Active results for pure compounds were reported as follows: cytotoxicity against ovarian cancer in mice: ginsenoside Rh_2[211]; L-1210 cells: panaxydol, panaxynol, panaxytriol[212,213]; MCF-7 breast cancer cells:

ginsenoside Rh_2.[214] Ginsenoside Rs_4 induced apoptosis in SK-HEP-1 cells; it significantly elevated levels of p53 and p21WAF1 and downregulated cyclin E- and A-dependent kinase activities.[215] Ginsenoside Rh_2 was found to induce apoptosis in C6Bu-1 cells; however, the expression of proapoptotic Bcl-2, Bcl-xl, and Bax was not altered by the compound, suggesting that there was another mechanism of apoptosis.[216] Panaxydol was reported to decrease proliferation of the human melanoma cell line, SK-MEL-1. It was found that the compound inhibited cell cycle progression at the G1-S transition; it also increased protein expression of p27 and decreased cyclin-dependent kinase 2 activity.[217] Panaxytriol was reported to inhibit DNA synthesis in and was cytotoxic against P388D1 mouse lymphoma cells, and it induced cell cycle arrest at the G2/M phase.[218] Ginsenoside Rg_3 inhibited the growth of the LNCaP prostate cancer cell line. The cells lost their adherent property; expression of PSA, androgen receptor, and 5-alpha-reductase genes was suppressed; apoptosis was induced; and Bcl-2 and caspase 3 expression were suppressed.[219] In a cancer chemoprevention assay, ginsenoside Rb_2 prevented the inhibition of gap junctional intercellular communication in WB-F344 rat liver epithelial cells by the tumor promoter 12-0-tetradecanoylphorbol-13-acetate.[220] Ginsenoside Rb_2 dose-dependently inhibited angiogenesis in B15-BL6 melanoma in syngeneic mice, although it did not directly affect the growth of melanoma or other tumor cells in vitro.

Inhibition of invasion and metastasis has been reported for various ginsenosides. Ginsenoside Rb_1 was found to be metabolized to a related compound by intestinal bacteria; this compound had an antimetastatic effect in Lewis lung carcinoma in mice.[221] The invasion of epithelial cells into basement membrane was reportedly inhibited by ginsenoside Rb_2.[222] Ginsenoside Rb_2 also inhibited invasiveness of endometrial cancer cell lines Ishikawa, HHUA, and HEC-1-A; these lines expressed matrix metalloproteinase MMP-2, which was suppressed by the ginsenoside. No effect was seen on the expression of tissue inhibitors of metalloproteinase.[223] Ginsenoside Rh_2, however, augmented metastatic potential of BALB/c 3T3 cells, while also suppressing carcinogen-induced initiation. The compound was without effect in the promotional stage of carcinogenesis.[224]

Combining *Panax* or its compounds with other agents has also been studied. A combination of ginseng extract with vitamin C synergistically inhibited mouse leukemic cell growth.[225] The saponin extract of *P. ginseng* increased proliferation of leukemic cells; however, in conjunction with homoharringtonine, cytarabine, adriamycin, or etoposide, the saponin extract significantly increased inhibition by cytotoxic drugs and sensitivity to the drugs.[226] *Panax notoginseng* increased tumor radiosensitivity in mouse KHT sarcoma. At lower doses of extract, normal bone marrow did not experience increases in radiosensitivity, although at higher doses, increased bone marrow toxicity was observed. Ginsenoside Rb_1, extracted from *P. notoginseng*, also increased tumor radiosensitivity, but increased bone marrow toxicity was not seen with the pure compound.[227] Mixtures of *P. ginseng* with other plant materials have also been studied. An aqueous preparation of a multicomponent traditional Chinese medicine tonic prescription containing a mixture of *Astragalus mongholicus*, *Cinnamomum cassia*, *Rehmannia glutinosa*, *Paeonia albiflora*, *Cnidium officinale*, *Atractylodes lancea*, *Angelica acutiloba*, *P. ginseng*, *Pachyma hoelen*, and *Glycyrrhiza* species was reported to have antileukopenic and anti-P-388 leukemia activities in mice.[228] The contribution of each of the component plant materials was not determined. The water decoction of a similar mixture of plant materials was reported to be active against the L-1210 leukemia in mouse.[229] Injury to mouse testis by doxorubicin was attenuated by an intestinal metabolite of ginseng through an antioxidant mechanism.[230] American ginseng, when used alone or concurrently with breast cancer therapeutic agents, was reported to inhibit the growth of MCF-7 breast cancer cells.[231] The combination of panaxytriol with mitomycin C (MMC), which is a reductive alkylating chemotherapeutic agent, showed synergistic effects in vitro.[232] Ginsenoside Rh_2 was found to potentiate the inhibitory effect of cisplatin on the growth of human ovarian cancer cells in mice when given on a daily basis; mice also survived longer when given the ginsenoside preparation.[233] Ginsenoside $Rh_2$and other *Panax* compounds enhanced the cytotoxicity of daunomycin and vinblastine in multidrug-resistant P388 leukemia cells.[234]

Studies on ginseng and cancer therapy in humans are rare. A German patent was obtained for the reported clinical effectiveness of the ginsenoside Rg_1 in the treatment of human stomach cancer.[235] Clinical research on ginseng revealed positive effects on the immune function of advanced stomach cancer patients, a possible explanation for a proposed anticancer effect.[236] In an open study, 126 cachectic cancer patients received a commercial combination product that contained ginseng[237]; improvements in fatigue, pain tolerance, mental concentration, physical activity, and appetite were reported.

More reports of human studies on ginseng and cancer focus on cancer prevention. Yun and colleagues[238] conducted 2 case-control studies of ginseng and cancer incidence in Korea. They found reduced relative risks of various cancers among ginseng users, ranging

from 0.57 to 0.20 for different forms of ginseng (fresh, white, and red). Smokers who took ginseng had lower risks of smoking-related cancers than those who did not.[238] Yun and Choi[239] conducted a prospective study in Korea of 4634 people older than the age of 40, from whom they obtained data on frequency and duration of ginseng intake in interviews. Ginseng consumers had a decreased risk of cancer (relative risk = 0.40); the risk of cancer rose with increasing levels of ginseng intake. For lung cancer and gastric cancer, the relative risks were 0.30 and 0.33, respectively. Preliminary clinical trials were carried out in Russia on tissue culture–derived ginseng extracts. Patients with chronic erosive esophagitis, a precancerous condition associated with esophageal cancer, were given ginseng extract in an open trial. Of 64 patients receiving ginseng, 73% experienced complete regression of erosion and inflammatory lesions, while only 16% of 19 control patients experienced complete regression. A small open trial of ginseng extract in patients with endometrial hyperplasia found that 3 patients with adenomatous-cystic hyperplasia experienced complete regression after 5 to 6 months of ginseng administration, while 8 patients with atypical hyperplasia experienced no regression. Of 9 control patients (both types of hyperplasia), none had a complete regression.[240] A double-blind randomized trial of red ginseng (1 g/day) in patients with chronic hepatitis C, who are at high risk for development of hepatocellular carcinoma, has been initiated; accrual is planned to be complete by January 2003.[241] This study was based on a previous intervention study using a Japanese Kampo formula, Sho-saiko-to, which showed some potential for prevention of hepatocellular carcinoma in hepatitis patients.[242] Use of the formula was associated with adverse effects (interstitial pneumonia); however, ginseng was not suspected of causing this effect based on a long history of safe use, and the randomized trial was thus planned for ginseng alone.

Antihyperglycemic Effect

Another important biological effect reported for *P. ginseng* or its saponins is hypoglycemic and antihyperglycemic activity.[114,115] The significance of elevated blood sugar and insulin levels in cancer is beginning to be recognized. Hyperinsulinemia and non-insulin-dependent diabetes mellitus (NIDDM) were observed to be related to incidence of colon cancer in Japanese men,[243] and a review article suggested that individuals with NIDDM are susceptible to a variety of malignancies, including those of the breast, endometrium, pancreas, and liver.[244] A synergistic effect of insulin and estradiol on the cell cycle of MCF-7 breast cancer cells has been observed.[245] In an Italian study, premenopausal women with higher levels of fasting glucose were at higher risk for breast cancer; the effect was also seen with postmenopausal women with body mass index greater than 26.[246] Normalization of insulin levels is thus of potential significance in the management of cancer risk and perhaps of cancer treatment. Research support for the hypoglycemic activity of ginseng and its components is increasing. Ginsenoside Rg_1 was reported to increase the number of insulin receptors rather than to change the receptor affinity.[247] Panaxan A was also reported as a main component for hypoglycemic activity of *P. ginseng*.[248] Research on the mechanisms of hypoglycemic activity suggested that panaxan B increased the plasma insulin level and enhancement of insulin sensitivity, while panaxan A worked by other mechanisms.[114] In a double-blind human trial, NIDDM patients were treated with ginseng or placebo; in the ginseng groups, blood glucose and body weight were reduced, while mood and psycho-physical performance were improved; a higher-dose ginseng group also showed improvements in glycated hemoglobin. The authors suggest that ginseng may be a useful adjunct in the treatment of NIDDM.[249] Lowered blood sugar after meals was observed in both normal and NIDDM subjects who took *P. quinquefolius* in a double-blind trial.[250] In subjects with normal glucose tolerance, *P. quinquefolius* was observed to reduce postprandial rises in blood glucose and reduce area under the glucose curve when compared with placebo in a randomized trial.[251] Time of administration of the ginseng preparation (120 minutes to 40 minutes prior to the test meal) did not affect the reduction in blood glucose levels.

Blood Coagulation Effects

A case of drug interaction between *P. ginseng* and warfarin was noted above[93]: ginseng was found to decrease effectiveness of warfarin. However, the effect of the plant extract itself, and its chemical constituents, is generally observed to be anticoagulant. Ginseng was observed to have antiplatelet activity related to inhibition of blood coagulation and enhancement of fibrinolysis. Panaxynol and ginsenosides R_0, Rg_1, and Rg_2 were reported as main components.[252] A ginsenoside fraction had an antithrombotic effect and decreased blood viscosity in rats subjected to thrombosis induced by adrenaline and cold stress.[253] Furthermore, the ginsenoside fraction had an inhibitory effect in rats on platelet aggregation induced by collagen or thrombin.[254]

Hormonal Effects

The reports of side effects such as vaginal bleeding or breast symptoms noted above under toxicity raise the possibility that ginseng might have estrogenic effects. Varied results on this question have been

obtained in laboratory and human studies: as with any herb or food, laboratory studies and studies of isolated components give only a restricted picture of functioning in the human body, so that studies of the whole herb are generally more credible than laboratory observations. The pleiotrophic effects of herbs and the variability of herbal constituents among different preparations must also be borne in mind in evaluating these and other studies of ginseng. Ginseng fed in the ration produced an estrogenic effect (increasing ceruloplasmin levels) in ovariectomized rats,[255] although the concentration in the diet may be higher than normal doses in humans. No in vitro binding to estrogen receptors was observed. A more recent study also observed no binding to the estrogen receptor in S30 breast cancer cells and no stimulation of alkaline phosphatase activity or progesterone receptor upregulation in Ishikawa endometrial cancer cells. It did demonstrate, however, induction of pS2, an estrogen-inducible gene, in the S30 cells.[256] Ginseng extract, observed to increase growth of estrogen-sensitive MCF-7 breast cancer cells by some investigators, nevertheless did not show activation of estrogen receptor-α or estrogen receptor-β or increase uterine weight in mice.[195] Ginsenoside Rg_1 increased H(3)-thymidine incorporation in MCF-7 breast cancer cells, although not in an estrogen receptor–negative cell line; it also stimulated an estrogen response element-luciferase reporter gene in HeLa cells. These 2 studies thus indicate phytoestrogenic activities for ginseng or ginseng compounds. Two clinical studies of ginseng extracts in postmenopausal women have been reported. A study in Japan examined 12 women who were not reporting menopausal symptoms and 8 women with symptoms.[257] They were treated with ginseng or placebo for 30 days. Women reporting menopausal symptoms (fatigue, insomnia, depression) who were treated with ginseng had improvements in the Cornell Medical Index and the State-Trait Anxiety Inventory. The ratio of cortisol to DHEA-S was also improved. A study from Norway randomized 384 postmenopausal women to ginseng or placebo treatment. Total scores on the Psychological General Well-Being Index (PGWB), the Women's Health Questionnaire, and visual analog scales did not differ between groups, although scores on the PGWB subscales for depression, well-being, and health were significantly higher in the ginseng group. Hot flashes were not reduced in the ginseng group. No differences were found for hormonally related physical variables such as FSH and estradiol levels, endometrial thickness, maturity index, or vaginal pH, indicating that for this preparation and dosage in the studied population, no hormonal effects were exerted on these tissues. No data were recorded on breast tissues.[258] These results raise questions about the estrogenic effect of ginseng, although the mixed results regarding the stimulation of MCF-7 cell growth still leave its effects on breast cancer unresolved. American ginseng and some ginseng constituents have been observed to suppress MCF-7 growth,[214,231] making it potentially of greater interest to breast cancer patients. The results of the Norwegian study, however, indicate an overall lack of estrogenic effect in the human body, implying a higher level of safety than the observations and laboratory reports.

Discussion: Clinical Potential of Ginseng

P. ginseng is used in some traditional Chinese medicine treatments for cancers and is of interest to cancer patients in other countries chiefly for its reputed antifatigue properties. Ginseng preparations are widely available from both traditional practitioners and commercial outlets such as health food stores. Ginseng is chemically complex; the ginsenosides are the most likely candidates for active compounds. While adulteration of this costly botanical medicine has long been suspected, recent analyses of commercial standardized extracts available in the US market indicate that such extracts have ginsenoside contents that generally correspond to the information shown on package labels.

The pharmacology of ginseng as it has been tested in animals and in humans has potential relevance for cancer patients. Concerns about toxicity do exist: excessive doses of ginseng may produce overstimulation or disturb sleep. Users who experience disturbed sleep have typically found that the problem resolves when ginseng is taken early in the day rather than in the evening. While the concerns about ginseng and hypertension seem grounded mainly in case reports rather than effects noted in clinical trials, patients with hypertension are usually counseled to avoid ginseng. There appears to be some evidence for estrogenic effects from case reports, which would indicate caution in use by patients with estrogen-dependent breast cancers. Laboratory studies of estrogenic effects have produced some conflicting results. Systematic studies of estrogenic effects in humans are too small to confirm or refute the possibility of estrogenic effects or effects on breast cells. Drug interactions have been reported and should be kept in mind when counseling patients about ginseng use. Many reports of ginseng toxicity are based on single case reports, often unsubstantiated with chemical analysis.

The immune, antistress, anticancer, and antifatigue properties of ginseng are of potential interest in its adjunctive use in cancer therapy. Stimulation of various immune system components, including the cytotoxic activity of NK cells, has been observed in

animal and human studies, although only one study demonstrating immunomodulatory effects in cancer patients has been located. Antioxidant activity has been confirmed in animals and humans: one animal study demonstrated protection of normal tissue against effects of doxorubicin based on antioxidant effects. Other preclinical studies have demonstrated increases in sensitivity to cytotoxic drugs with some ginseng extracts or compounds. A number of animal models of physical, chemical, and biological stress have been used to demonstrate protective effects for ginseng. Protection against adverse effects of radiation has been reported, as has increased tumor radiosensitivity in an animal model. Potential cytotoxicity of ginseng has been assayed in many cancer cell lines, with mixed results. Several of the ginsenosides have demonstrated interesting anticancer activities in vivo and in vitro, including induction of apoptosis, inhibition of cell cycle progression, and antiangiogenic activity. None, however, have yet been studied preclinically as new leads for drug development. Ginseng users in Korea had a lower incidence of cancer than did nonusers in a prospective study, indicating a potential cancer preventive activity; however, the correlation of ginseng use with other dietary patterns that might affect cancer incidence cannot be ruled out in such a study. Open trials of ginseng in precancerous conditions in Russia have indicated interesting preliminary results, and the use of ginseng for chemoprevention of hepatocellular carcinoma in hepatitis C patients is being studied in a randomized trial. The antihyperglycemic effect of ginseng may be of potential relevance in cancer management, as NIDDM has been observed to be correlated with increased cancer incidence and elevated insulin levels may stimulate growth of tumors. Research on use of ginseng in managing fluctuations in blood sugar and insulin in cancer patients could be explored.

Although the above pharmacological properties suggest that ginseng may contribute, in ways that are not yet completely clear, to cancer control, the more typical goal of ginseng use in cancer treatment is to counteract fatigue and debility. An open study of a compound preparation containing ginseng in cancer patients did report improvements in fatigue, mental concentration, and other variables. Some recent randomized trials of ginseng alone or in combination with ginkgo indicate potential for improvement of memory. The antifatigue properties of ginseng in humans who are weak, ill, or convalescent has not yet, however, been validated in randomized studies. Many randomized studies have been conducted on ginseng or compound preparations containing ginseng in basically healthy populations, with inconclusive results. Design of many of the studies has been poor. It is thus not possible to either rule out or confirm the usefulness of ginseng on the fatigue and debilitation experienced by cancer patients at this time. Patients may thus wish to try ginseng empirically as an adjunct to other cancer treatments. In this case, the health care professional should ensure that no contraindications are present, that the patient is using a reliable standardized product that actually contains *P. ginseng*, and that ginseng dosing does not interfere with sleep patterns. The patient may then be helped to self-monitor in a systematic way, such as daily recording of perceived fatigue levels with and without ginseng use, to determine whether this ancient remedy, employed for centuries by a population experienced in the use of many herbal remedies, has a role in his or her present-day integrative cancer treatment protocol.

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