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COMMENTARY

Panax ginseng Pharmacology: A Nitric Oxide Link?

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ABSTRACT. *Panax ginseng* is used in traditional Chinese medicine to enhance stamina and capacity to cope with fatigue and physical stress. Major active components are the ginsenosides, which are mainly triterpenoid dammarane derivatives. The mechanisms of ginseng actions remain unclear, although there is an extensive literature that deals with effects on the CNS (memory, learning, and behavior), neuroendocrine function, carbohydrate and lipid metabolism, immune function, and the cardiovascular system. Reports are often contradictory, perhaps because the ginsenoside content of ginseng root or root extracts can differ, depending on the method of extraction, subsequent treatment, or even the season of its collection. Therefore, use of standardized, authentic ginseng root both in research and by the public is to be advocated. Several recent studies have suggested that the antioxidant and organ-protective actions of ginseng are linked to enhanced nitric oxide (NO) synthesis in endothelium of lung, heart, and kidney and in the corpus cavernosum. Enhanced NO synthesis thus could contribute to ginseng-associated vasodilatation and perhaps also to an aphrodisiac action of the root. Ginseng is sold in the U.S. as a food additive and thus need not meet specific safety and efficacy requirements of the Food and Drug Administration. Currently, such sales amount to over $300 million annually. As public use of ginseng continues to grow, it is important for this industry and Federal regulatory authorities to encourage efforts to study the efficacy of ginseng in humans by means of appropriately designed double-blind clinical studies. BIOCHEM PHARMACOL **54**;1:1–8, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. *Panax ginseng*; food additive; nitric oxide; endothelium; corpus cavernosum; ginsenosides; phytomedicinals; herbal medicine

This Commentary will provide some general observations on the use and study of ginseng and will also describe recent experiments which suggest that its cardiovascular actions may reflect, in part, increased synthesis of NO†.

BACKGROUND

Use of *Panax ginseng* (Fig. 1) has a long and rich history in traditional Chinese medicine. Prized by practitioners of Chinese medicine, and their patients, as an effective "tonic," ginseng has been in use since the Han Dynasty some 2000 years ago and perhaps even longer. As might be expected of this venerable herb, there is an extensive literature focusing on its use. Contributions range from anecdotal, descriptive clinical observation to detailed study of individual constituents by modern techniques of molecular biology. One also finds folklore and romanticism which offer illuminating glimpses of a system of beliefs and practices that form the background to the study of ginseng. However, the more lavish and even mystical claims for ginseng do little to clarify its mechanism of action in a manner that can satisfy—or even conform to the "rules" of—Western biomedical science. Nevertheless, the preponderance of evidence from studies with a variety of experimental animals must lead the unbiased reader to conclude that authentic, standardized ginseng does indeed enhance stamina and physical capacity, especially when these are compromised. Data from clinical studies are less convincing, although public enthusiasm for herbal and other "unconventional" remedies continues to grow in this country [1] and throughout the world [2]. In several European countries, ginseng and other phytomedicinals are prescribed by physicians, and elements of botanical medicine are again being taught in medical schools. In its Commission E Monographs, which set standards for safety and efficacy of medicinal herbs, the German government recognizes use of ginseng as a tonic "for invigoration and fortification during times of fatigue and debility".*

Sale of Ginseng in the United States

Panax ginseng figures prominently among sales of botanical products in the United States, which total about $1.5 billion annually [3]; of the latter figure, ginseng comprises 15–20%. At present in this country, ginseng preparations are sold as food additives rather than therapeutic agents

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† *Abbreviations:* NO, nitric oxide; ACh, acetylcholine; and 5-HT, 5-hydroxytryptamine.

* Foster S, Asian Ginseng, *Panax ginseng*: American Botanical Council. Botanical Series, No. 303, pp. 3–8, 1996.

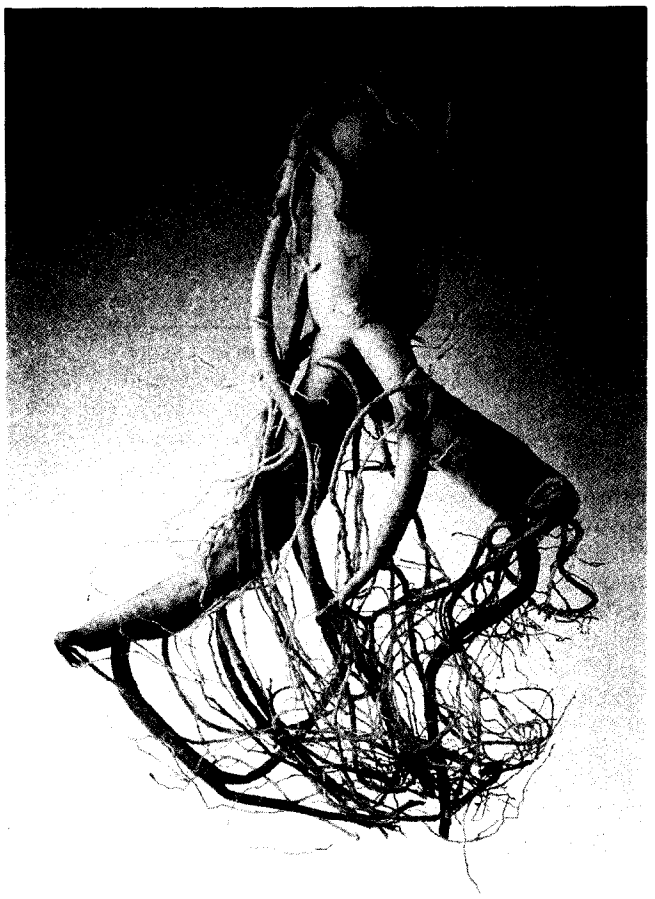


FIG. 1. Root of *Panax ginseng*. The photograph was provided by Dr. Fabio Soldati, Pharmaton SA, Lugano, Switzerland.

and, therefore, are subject only to requirements of the Dietary Supplement Health and Education Act of 1994. Accordingly, they make no claim of therapeutic efficacy (which would require approval of ginseng as a drug by the Food and Drug Administration), and ginseng from many manufacturers can be and is sold freely. Thus, the composition of preparations sold can vary widely, and, indeed, some preparations of "ginseng" do not contain any active component ginsenosides [4]. The ethical food additive manufacturers, the FDA, and legislative authorities are engaged in a continuing dialogue that should encourage effective regulation of ginseng and other botanical preparations sold in this country. A major problem in this regard is the fact that even standardized ginseng preparations (see below) are mixtures of many chemical entities. Thus, it is difficult to establish their efficacy by conventional pharmacological means. However, it is obviously important to provide the public with reliable information about the ginsenoside content of ginseng samples and their clinical efficacy established by acceptably designed clinical studies.

Chinese medicine differs from conventional Western medicine in several respects (Table 1). Perhaps the most significant difference is that botanically based therapy is used by Chinese medicine to maintain health, although, of course, treatment of disease is also its goal. The preventive

TABLE 1. Some differences between Chinese and Western medicine*

Chinese medicine	Western medicine
Uses plants, often complex mixtures of plants.	Uses single chemically defined drugs when possible.
Goal is to maintain health and "harmony" between patient and environment.	Goal is to cure disease, eliminate causative agents, ameliorate symptoms.
Least successful in advanced disease or trauma.	Very successful in treating selected diseases.
Least toxic agents preferred.	Specific agents used where possible. Side-effects may be the "price" of treatment.

* After Fulder [5].

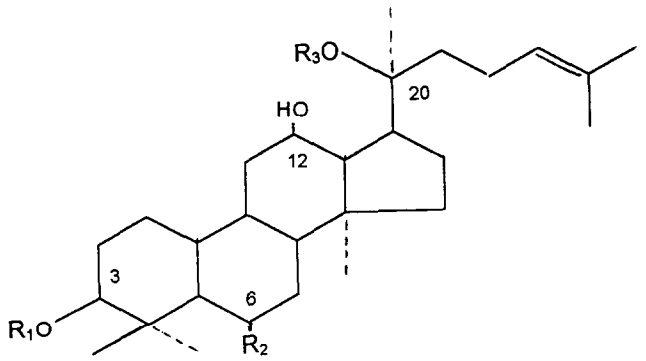
philosophy of this and other traditional systems of medicine is gaining much support in this country. In a recent issue of *Biochemical Pharmacology* [6], Pezzuto argues for the creation of a national program for prevention or inhibition of carcinogenesis by plants or plant-derived preparations. In this favorable climate, public enthusiasm for herbal medicine is likely to continue its rapid growth.

Sources and Preparation of Ginseng

Named by botanist Carl Meyer in 1842, the genus *Panax* derives its name from the Greek *pan* (all) and *akos* (healing), literally all-healing or panacea. This derivation together with its lack of specificity (see Table 1) and some of the broad claims made for the virtues of ginseng almost guarantee skepticism in Western scientific and medical circles. *Panax ginseng* or Asian ginseng from Korea and Eastern China is one of several species of the genus *Panax* (fam. Ariliaceae), which also includes *P. quinquefolius* (American ginseng) primarily from Wisconsin and British Columbia and the less frequently encountered *P. notoginseng* and *P. japonicus*. In the United States and Europe, ginseng is usually found as a preparation of the root of *P. ginseng* or *P. quinquefolius*. Another common preparation is *Eleutherococcus senticosus* or Siberian ginseng, which is a member of the Ariliaceae family but contains chemically distinct glycosides (eleutherosides [7]). *Panax ginseng* in this country and Europe is mainly imported from Korea, where it is cultivated extensively. Roots of 5- to 7-year-old plants are either air-dried yielding "white ginseng" or steam-treated for 2–4 hr giving rise to "red ginseng." Data from the United States Department of Commerce indicate that over 1 million pounds of ginseng were imported into this country in 1994. Interestingly, *P. quinquefolius* or American ginseng from Wisconsin and Western Canada represents a $150 million crop exported particularly to China, where disappearance of the wild *P. ginseng* has made cultivated American ginseng highly regarded by users.

Chemistry

Consensus opinion [8, 9] suggests that the major active principles of *P. ginseng* are ginsenosides (glycosides), deriv-



20(S)-protopanaxadiols

Ginsenoside	R_1	R_2	R_3	% in Root
Rb_1	Glc^2-Glc-	H	Glc^6-Glc	0.38
Rb_2	Glc^2-Glc-	H	Glc^6-Ara(p)	0.13
Rc	Glc^2-Glc-	H	Glc^6-Ara(f)	0.19
Rd	Glc^2-Glc-	H	Glc	0.04

20(S)-protopanaxatriols

Ginsenoside	R_2	R_2	R_3	% in Root
Re	H	-O-Glc^2-Rha	Glc-	0.15
Rf	H	-O-Glc^2-Glc	H:20(S)	0.09
Rg_1	H	-O-Glc-	Glc-	0.38
Rg_2	H	-O-Glc^2-	H:20(S)	0.02

FIG. 2. Structures of main ginsenosides of *Panax ginseng* [10, 11].

atives of the triterpene dammarane structure (see Fig. 2). Minor components include amino acids, peptides, and minerals. Over 20 ginsenosides have been extracted from roots, leaves, and flower buds of ginseng. Aglycones of the common ginsenosides are 20(S)-protopanaxadiol (Rb_1, Rb_2, Rc, and Rd) or 20(S)-protopanaxatriol (Re, Rf, Rg_1, and Rg_2) structures (Fig. 2). Nomenclature derives from the mobility of these ginsenosides in a one-dimensional thin-layer chromatographic system [10, 11]. Sugar moieties found are glucose, maltose, fructose, and saccharose. Methods for the purification and quantitation of ginsenosides by conventional HPLC, as well as electrospray HPLC and mass spectrometry, are now available [10–12]. Analysis revealed that the ginsenoside content depends on the species of ginseng, the manner of sample preparation, and the age and part of the plant extracted [10, 11]. Likely therefore, some of the conflicting data in the ginseng literature reflect differences in ginsenoside content among samples of ginseng used in different laboratories. A 1978 study of 23 commercial samples of ginseng [13] by thin-layer chromatography revealed that 8 of the samples did not contain *any* ginseng.

To address this problem and to provide the public with reliable information on ginseng preparations available, the American Botanical Council (a non-profit organization in Austin, TX) has sponsored a carefully controlled analysis of several hundred ginseng products on the market. Samples are identified only by number and are analyzed in two independent, academic chemistry laboratories by means of standard HPLC techniques [10]. Results of this study are to be published in 1997 and should encourage the use of standardized ginseng samples both by the public and in research. Also expected to promote the use of authentic ginseng samples in research are recently described methods for identification and differentiation of *P. ginseng*, *P. quinquefolius* and *P. notoginseng* by random-primed polymerase chain reaction (PCR) and DNA "fingerprinting" [14].

It is clearly important to use either individual ginsenosides or preparations with known ginsenoside content in research studies. One sample of ginseng used in many studies, including some from the author's laboratory [15], is G115© or Ginsana©, which is standardized to contain 4% ginsenosides [10].

Adaptogenic Effects of Ginseng

Chinese traditional medicine considers ginseng to have salutary effects on physical capacity, alertness, and power of concentration, especially in the elderly and those recovering from illness [5, 8]. It is also used by athletes to enhance their "energy level" [16]. Brekhman, a pioneer in the experimental evaluation of ginseng, used the term *adaptogen* to describe these non-specific "tonic" effects of *P. ginseng* and other members of the Ariliaceae family [7]. It was noted that effects of ginseng were particularly evident "when the resistance of the organism was diminished or . . . was taxed with extra demands" [7]. Thus, they found that ginseng was more effective than a placebo in enhancing running performance of young adults and found that radio operators made fewer transmission errors after ginseng. It has often been confirmed in clinical evaluation [8, 11, 17], that the actions of ginseng are less evident in non-stressed human subjects or experimental animals. Ginseng reportedly increased resting oxygen uptake and oxygen transport in elderly subjects [16] and significantly increased the capacity for mental arithmetic and logical deduction in healthy normal subjects [18], although tests of motor coordination and visual reaction times were unaltered. A careful study by Pieralisi *et al.* [19], using a double-blind cross-over design, revealed that ginseng significantly increased work load and oxygen uptake in normal subjects. Also, at a fixed work load, ginseng decreased oxygen consumption, carbon dioxide production, and plasma lactate [19]. Bahrke and Morgan, in reviewing the ergogenic properties of ginseng in athletes, pointed out [16] that the design of many studies did not include the placebo-treated controls or double-blind design that is essential to establish efficacy in a reliable manner. Within these limitations, there are several clinical reports suggesting increased physical performance and reduced fatigue in human subjects [11, 17–19].

Not surprisingly, much research effort also has focused on the mechanism of the adaptogenic properties of ginseng in experimental animals (see Refs. 8, 9, and 16 for review). Unfortunately, many of these studies are not available in English language journals, and those abstracts that are

available in translation rarely permit evaluation of methodology or—most importantly (see above)—qualitative and quantitative data on ginsenosides present when total root extract was used.

As with human subjects, adaptogenic actions of ginseng are particularly evident when the organism is challenged by a wide variety of physical, chemical, or biological influences [16]. Experimental animals are reported to show enhanced resistance to X-irradiation, viral and tumor load, temperature stress, hyperbaric hyperoxia, and physical exercise [7, 9, 16]. Some of these effects are attributed to actions on the hypothalamic-pituitary-adrenal system [9, 20], and there is evidence that ginseng increases plasma immunoreactive adrenocorticotropic hormone (ACTH) and corticosterone after its i.p. injection in rats [21]. These effects were eliminated by hypophysectomy [21]. There is an extensive literature describing work with experimental animals which points to actions on the immune system or the central nervous system [16, 22]. Lacking, however, is a detailed, appropriately controlled, double-blind clinical trial of ginseng action on immune function. Experiments with animals have also demonstrated central effects of ginseng. For example, rats treated orally with 20 mg ginseng root extract (G115) per kg per day for 3 days showed improved performance in behavioral tests designed to assess memory enhancement and retention. If the dose of ginseng was increased to 50 mg/kg for 5 days, brainstem dopamine and norepinephrine were increased while serotonin was increased in the cortex [23]. The same author found that the serotonin receptor (5-HT_3) agonist 2-methyl 5-HT abolished this action as did the specific 5-HT_{1A} antagonist 8-hydroxy-2(di-*n*-propylamino) tetraline hydrobromide and, therefore, concluded that serotonergic transmission is involved in the memory-enhancing action of ginseng [24]. Other authors also have implicated serotonergic or dopaminergic mechanisms in the effects of ginseng on behavioral parameters [25]. Bhattacharya and Mitra [26] reported that both white and red varieties of ginseng (20 and 50 mg/kg administered twice daily for 5 days) reduced conflict behavior in rats and footshock-induced fighting in paired mice. Ginseng also attenuated pentylenetetrazole-induced decrease in rat brain monoamine oxidase (MAO) activity, proposed as an endogenous marker for anxiety, confirming its tranquilizing or anti-anxiety effect. In fact, actions of white and red ginseng after 5 days of treatment were comparable to those of diazepam.

CARDIOVASCULAR ACTIONS AND POSSIBLE MEDIATION BY NO

Cardiovascular effects of ginseng root and individual ginsenosides have been studied extensively. Many reports describe transient vasodilator actions, in some cases followed by vasoconstriction and increase in blood pressure. Several authors have implicated the adrenergic nervous system in the cardiovascular effects of ginseng [27], and it was reported recently [28] that the panaxatriols, particularly Rg_2, reduced ACh-evoked release of catecholamines from bovine adrenal chromaffin cells. Extrapolating from these data, the authors suggest that ginseng may reduce elevated circulating catecholamine concentrations associated with various forms of stress in humans.

The complex cardiovascular actions of ginseng *in vivo* could reflect differing ginsenoside content of the extract used (see above) or the method of its extraction. Lee *et al.* [29], working with anesthetized dogs, noted that i.v. administration of ethanol or ether extract of ginseng (40 mg/kg) decreased total peripheral resistance and caused vasodilatation and bradycardia, while a similar dose of aqueous extract increased total peripheral resistance.

We questioned [30] whether some of these complex vascular effects might reflect the qualitative and quantitative heterogeneity [7, 9] of ginsenoside action on different vascular beds that also could be observed *in vitro*. Total *P. ginseng* root extract did not alter basal vascular tone in ring preparations of vessels from rabbits, dogs, and humans but relaxed vessels precontracted with either norepinephrine (rabbit pulmonary and intrapulmonary artery) or prostaglandin $F_{2\alpha}$ (rabbit lung vessels and canine mesenteric vein). We therefore suggested [30] that these actions could reflect the interaction of ginseng with an endogenous vasoactive substance. Although unknown at the time, it now appears that a likely candidate is NO released from endothelial cells (see below).

NO and Antioxidant Actions

Much evidence points to a close link between damaging actions of free radicals of oxygen and many forms of human disease [31], including cardiopulmonary pathology and reperfusion ischemia in heart and lung. It is therefore interesting that ginseng, an important component of a traditional Chinese mixture of herbs used to treat coronary artery disease and myocardial infarction [32], has well recognized antioxidant actions [33]. For example, ginseng had protective effects in experimental infarction (coronary ligation for 1 hr) in dogs. This effect could also be demonstrated with neonatal rat cardiac myocytes in culture exposed to oxidant injury. Ginseng root extract significantly reduced lactic acid dehydrogenase release from these cells during anoxia and reoxygenation [32]. Antioxidant properties have also been reported in experiments with ischemia–reperfusion injury in rat brain [34].

In the circulatory system, the vascular endothelial cell is an early focus of free radical injury. We therefore explored the protective action of ginseng with a pulmonary model in which endothelial injury is caused by a variety of reduced oxygen species. In this method, a modification of the technique described by Jackson *et al.* [35], oxygen free radicals, including superoxide and hydroxyl radicals, are generated in solution by brief electrolysis of medium perfusing rabbit lungs *in vitro* [36]. Such treatment decreases the synthesis of NO and reverses the normal vasodilator response to ACh in lungs preconstricted with a thrombox-

ane analog, U46619 [36, 37]. Ginsenoside (50 or 200 μg/mL) prevented these vascular effects and also reduced the pulmonary edema that follows free radical injury [38]. The latter effect was eliminated by 100 μM nitro-L-arginine, an inhibitor of NO synthase. These data are consistent with the proposal that ginseng causes vasorelaxation and prevents manifestations of oxygen free radical injury by promoting release of NO.

In support of this proposal, we found that conversion of [^{14}C]L-arginine to [^{14}C]L-citrulline in confluent bovine aortic endothelial cells in culture was enhanced significantly by ginseng and by Rg_1 but not by Rb_1 [38]. Bradykinin, known to activate NO synthase in endothelial cells, also increased [^{14}C]citrulline production [38]. Because ginseng is used orally, we determined whether similar actions would be seen after digestion designed to mimic the pH exposure after oral ingestion. We incubated standardized total root extract (G115) at 37° for 1 hr in saline at pH 1.2 and then for 5 hr at pH 6.75 [15]. As a control, we used G115 incubated instead with water. After neutralization and lyophilization, the product was used in experiments similar to those described above [38]. Both digested and undigested ginseng dilated preconstricted perfused lung and preserved ACh dilatation following free-radical injury [15]. Ginsenosides Rg_1 and Rb_1 were much less effective vasodilators after similar digestion [15], suggesting that standardized extracts of ginseng may be more effective after oral administration than individual ginsenosides.

Recently, it was reported* that treatment of rats with standardized ginseng extract (10 mg/mL of drinking water for 7 days) had cardioprotective effects that could be demonstrated *in vitro*. After treatment with ginseng or water only (as control), animals were exposed to hyperbaric hyperoxia (100% O_2; 2.5 atm for 6 hr). Hearts from G115-treated rats perfused *in vitro* by the Langendorff technique showed significantly lower coronary vasoconstriction in response to angiotensin II than control hearts. Also, endothelial function in aortic rings from ginseng-treated animals was preserved, as evidenced by normal relaxation in response to ACh and a modest vasoconstriction after inhibition of NO synthase. Both observations imply protection of endothelial function from oxygen radical damage. Therefore, this study confirms and extends data of Kim *et al.* [38] by establishing that oral administration of a standardized ginseng provides significant antioxidant action and may also stimulate NO synthase.

Antioxidant properties of ginseng root aqueous extract also have been noted with a 0.1 M HEPES buffer model system. The ginseng extract (equivalent to 100 μg of original root) significantly inhibited iron-mediated peroxidation of arachidonic acid [39] in this system and hydroxyl radical formation from added hydrogen peroxide. Unfortunately, individual ginsenosides were not used by these authors. It would be of considerable interest to know whether Rg_1 also showed this antioxidant action to a more marked degree than Rb_1, as reported by Kim *et al.* [38].

The cardioprotective action of ginseng against ischemia–reperfusion injury has been reported in a study of patients undergoing cardiopulmonary bypass for mitral valve surgery [40]. Among 30 patients studied, 11 received normal cardioplegic solution (used to suspend cardiac action during phases of the surgical procedure), 11 received a solution with ginseng extract (0.6 to 1.2 mg/kg) and 8 received a solution containing ginsenosides Rb_1 and Rb_2 (0.3 to 0.6 mg/kg). Cardiac performance was monitored by the esophageal Doppler technique and also by morphometric analysis of samples of left ventricular myocardium. Total ginseng extract enhanced recovery of cardiac hemodynamic performance and significantly lowered mitochondrial swelling during the period of ischemia. Interestingly, and not uncommon in ginseng literature, total root extract in these studies was more effective than the individual ginsenosides used. Unfortunately, the nature of the ginseng extract (type, extraction technique) is not stated. Nevertheless, this study is intriguing and awaits independent confirmation.

Several observations suggest that release of NO by ginseng may underlie the antioxidant effect of the extract. Thus, NO-releasing agents protected Chinese hamster lung fibroblasts (V79 cells) from oxy-radical damage caused by hypoxanthine/xanthine oxidase [41], implying that NO, perhaps at low concentration, need not be cytotoxic. A recent report [42] indicates that the protopanaxadiols Rb_1 and especially Rb_2 enhanced expression of the Cu,Zn-superoxide dismutase gene, likely mediated by the AP2 transcription factor. If demonstrated also to occur in vascular cells, this effect may contribute to the antioxidant action of ginseng.

Support for the proposal that ginseng might enhance NO synthesis comes also from experiments with extrapulmonary vascular and non-vascular systems. Ginsenosides Rg_1, Rb_1, and Re caused endothelium-dependent relaxation in rat aorta and increased synthesis of cyclic GMP (cGMP) [43]. In contrast, Rb_1 and Rc had neither action. A single i.p. injection of ginseng extract (200 mg/kg) increased nitrites, nitrates, and cGMP levels in rat serum and urine [44]. These effects were reversed by inhibition of NO synthase and restored by L-arginine. Similar action was seen with rat kidney, isolated glomeruli, and cortical tubules and was blocked by inhibition of NO synthase. The authors concluded [44] that ginseng extract stimulates NO production in the kidney and thus may protect against ischemia by increasing renal blood flow. Kang *et al.* [45] found that addition of ginseng to a high cholesterol diet fed to rabbits preserved most of the normal dilatation of preconstricted aortic rings in response to ACh. Interestingly, ginseng did not change endothelium-dependent relaxation to ACh in animals receiving a normal diet. The mechanism of this effect is unknown but could reflect enhanced NO produc-

* Maffei-Facino R, Carini M, Aldini G and Calloni MT, *Panax ginseng* protects rat heart from ischemia–reperfusion damage induced by hyperbaric oxygen. Poster P-42. *Proceedings of the Second International Conference on Phytomedicine*, April 11–14, 1996, Munich, Germany.

tion or some enhancement of the guanylate cyclase path. Therefore, it would be appropriate to determine whether ginsenoside affects expression of NO synthase and guanylyl cyclase genes.

Ginseng Aphrodisiac Action

Ginseng has long been reported to have aphrodisiac properties [5, 11, 32]. To a significant degree, it is likely that such effects reflect the non-specific "tonic" or adaptogen actions referred to above. However, recognition of the importance of NO in the mechanism of penile erection [46] led to consideration [47] of a possible ginseng–NO link using the corpus cavernosum of the rabbit as a model. NO is released from non-adrenergic, non-cholinergic (NANC) nerves and relaxes both human and rabbit [46–48] penile corpus cavernosum, thus permitting penile erection. Since endothelial cells and perivascular nerves in the corpus cavernosum contain NO synthase, ginsenosides may relax the corpus secondary to release of endogenous NO. By means of an *in vitro* superfusion technique, Chen and Lee [47] found that ginseng extract relaxed the corpus cavernosum in a concentration-dependent manner, increased ACh-induced relaxation, and significantly enhanced tetrodotoxin-sensitive cavernosal relaxation in response to transmural nerve stimulation. These effects were attenuated significantly by inhibition of NO synthase and were enhanced by superoxide dismutase, which is assumed to scavenge oxy-radicals that would otherwise oxidize NO. The authors concluded that ginsenosides may release NO from endothelial cells and perivascular nitrergic nerves in the corpus cavernosum and speculated that the aphrodisiac effect of *P. ginseng* may be linked, in part, to release of NO. Clearly, these findings invite confirmatory experiments with human tissue.

Recent studies therefore suggest that some effects of ginseng in experimental systems may be explained by the enhanced presence of NO. Evidence has been offered that (1) ginseng enhances formation of citrulline from added arginine, implying enhanced synthesis of NO, (2) known inhibitors of NO synthase, including oxyhemoglobin and substituted arginine derivatives, block both the action of ginseng on citrulline formation from arginine and ACh-induced vascular relaxation of preconstricted tissue, (3) when used, arginine reverses the action of NO synthase inhibitors, and (4) when measured, tissue cGMP has been increased by ginseng.

Side Effects of Ginseng

In view of widespread use of ginseng, it is appropriate to conclude this Commentary with some observations concerning published clinical reports of ginseng toxicity. The LD_{50} of ginseng root in mice has been reported to be 10–30 g/kg [7]. Chronic treatment of rats, mice, dogs, and rabbits has shown very few observable signs of toxicity. There were no treatment-related changes in body weight, hematology, or clinical chemistry [49] after 90 days of daily administration of as much as 15 mg/kg to both male and female dogs. Despite the expectation of safety that such data might generate, case reports of presumed ginseng toxicity continue to appear in the literature. Parenthetically, it should be noted that many such reports are difficult to evaluate because they do not provide information about the form or manufacture of ginseng used or indeed whether the preparation actually contained ginseng [4]. In a 2-year study [50], 14 of 133 subjects reported nervousness, insomnia, and gastrointestinal disturbance associated with prolonged consumption of doses (up to 15 g/day) that were much higher than those recommended. Also, the study design in this case did not use a placebo, it called for self-evaluation of side-effects by the subjects, and the paper describes neither the form of ginseng used nor its qualitative identity. As with clinical studies of efficacy, it is essential that side-effects attributed to ginseng preparations must be accompanied by information on the content of ginsenosides. It is also notable that many reports of toxicity originate in those countries that lack medico–legal regulation of ginseng use [9] and thus leave consumers exposed to variability in the quality of ginseng available. In contrast, reports of toxicity are rare in Germany and other European countries in which ginseng is medically prescribed and is used in recommended doses. Indeed both the World Health Organization and the Commission E conclude that, in recommended doses, there are no known side-effects of ginseng. Unfortunately, there are relatively few clinical studies of ginseng that have used controlled double-blind design. Such studies are essential if there is to be broad acceptance by Western medicine. Despite the fact that skepticism remains among medical practitioners in this country regarding its efficacy, use of ginseng (and other) botanicals by the public continues to grow. It is therefore appropriate to question whether the designation of ginseng as a food additive is appropriate. It seems important for the food additive industry and governmental authorities to actively encourage efforts to study ginseng efficacy in humans by means of appropriately designed, longer term clinical studies. While studying safety and efficacy, however, it should be recognized that ginseng derives from a culture and philosophy in which prevention of illness rather than its treatment is of the essence.

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