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Is ginseng free from adverse effects?

Jing-Tian Xie[1,2], Sangeeta R. Mehendale[1,2], Spring A. Maleckar[1,2] and Chun-Su Yuan [1,2,3,*]

[1]*Tang Center for Herbal Medicine Research;* [2]*Department of Anesthesia & Critical Care,* [3]*Committee on Clinical Pharmacology, The Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637*

SUMMARY

Ginseng is a perennial herb widely used in China, Japan, and Korea. It is also one of the most commonly used herbal medicines in the U.S. Although it is generally considered safe to use, adverse effects associated with ginseng use have been reported. Inappropriate ginseng use, such as high dose administration, may cause insomnia, headaches, diarrhea, as well as cardiovascular and endocrine disorders. Other factors that may contribute to adverse effects of ginseng include the variety of ginseng species, variability in commercial ginseng preparations, and potential ginseng-drug interactions. To minimize adverse effects of ginseng, consumers should be advised to use it appropriately, and the herbal industry should try to provide standardized ginseng preparations.

Key Words: Ginseng; Ginsenosides; Commercial preparation; Side effect; Adverse effect

INTRODUCTION

Ginseng is a deciduous perennial plant belonging to the Araliaceous family. Respected as a "king herb" in the East, ginseng has been one of the most widely used in traditional Chinese medicine for several thousand years (Keum *et al.*, 2000; Kim *et al.*, 2002). In oriental countries, ginseng has been used as a general tonic and to maintain, restore or increase health, vitality, and longevity. It was reported that Marco Polo was aware of Chinese ginseng, and the plant was brought to Europe possibly with the silk trade, and it is certain that the Arabs brought back ginseng from China in the 9th century (Phillipson and Anderson, 1984). Currently, ginseng is also one of the most commonly used herbal medications in the West (Vogler *et al.*, 1999; Kaufman *et al.*, 2002).

Research data demonstrated that ginseng and its major active components, ginsenosides, have a complex constitution and multiple pharmacological actions (Attele *et al.*, 1999). Ginseng and ginsenosides influence the central nervous system (including learning, memory, and behavior), as well as cardiovascular, gastrointestinal, endocrine and immune systems (Attele *et al.*, 1999; Yuan *et al.*, 2001; Kim *et al.*, 2002). It is commonly accepted that ginseng administration, in general, is safe when used appropriately (Singh *et al.*, 2001; Ernst, 2002). However, like all other herbal medications, ginseng contains a number of identified and unidentified chemical constituents with or without pharmacological activities. We have studied the beneficial effects of ginseng in different organ systems (Yuan *et al.*, 1998a; Yuan *et al.*, 1998b; Yuan *et al.*, 1999, Attele *et al.*, 1999; Liu *et al.*, 2001; Yuan and Dey, 2001; Yuan *et al.*, 2001; Attele *et al.*, 2002; Xie *et al.*, 2002a; Xie *et al.*, 2002b). In this article, we will discuss potential adverse effects of ginseng, especially when ginseng was consumed inappropriately or abused (e.g., ginseng abuse syndrome), or due to the lack of quality control in ginseng products (Siegel, 1979; Dega *et al.*, 1996; Faleni and Soldati, 1996; Nocerino *et al.*, 2000; Morgan and Cupp, 2000; Ang-Lee *et al.*, 2001a; Yuan *et al.*, 2002). Ginseng animal toxicity data will also be reviewed.

*Correspondence: Chun-Su Yuan, MD, PhD, Department of Anesthesia & Critical Care, The University of Chicago, 5841 S. Maryland Avenue, MC 4028, Chicago, IL 60637, U.S.A. Tel: 82-73-702-1916; Fax: 82-73-834-0601; E-mail: cyuan@midway.uchicago.edu

TOXIC EFFECTS IN ANIMAL STUDIES

Acute toxic effect

Data indicated that the LD_{50} of ginseng root extract in mice was 5 g/kg after oral administration (Huang, 1999). In another report, LD_{50} of the root was 10-30 g/kg in mice (Brekhman and Dardymov, 1969). The LD_{50} of ginseng leaf and stem extract was approximately 625 mg/kg i.p. injection in mice (Wang *et al.*, 1982), and the LD_{50} of crude saponin fraction and saponins of ginseng leaf was 381 and 299 mg/kg after i.v., respectively. Behavioral changes observed after administration of lethal doses showed that crude saponin fraction produced extended posture with the abdomen of the mice touching floor and abnormal gait a few minutes after i.p. injection. Approximately 10 min later, swimming convulsions appeared and mice died after 15-25 min. The LD_{50} was approximately 300 mg/kg (Saito *et al.*, 1973). Variable ginseng extracts contribute to the inconsistent LD_{50} data, making direct comparison impossible.

Our laboratory also evaluated the acute toxicity of ginseng berry extract in *ob/ob* mice. No adverse effects were observed in six animals who received 500 mg/kg daily i.p. injection for 12 days, while the maximum daily therapeutic dose used in other studies was 150 mg/kg (Xie *et al.*, 2002b). However, all four *ob/ob* mice died within 24 hours after receiving a single i.p. dose of the extract at 1500 mg/kg (Yuan *et al.*, unpublished data).

Subacute toxic effect

In rats, ginseng leaf and stem extract at doses up to 80 mg/kg, i. p. for 21 days did not affect blood cells, hemoglobin levels, or renal function (Wang *et al.*, 1982). In another subacute study, there were significant increases in body weight and food consumption in rats, while the brain, heart, lung, liver, spleen, kidneys stomach, testis/ovaries were normal in both gross and histopathological examination (Aphale *et al.*, 1998).

Chronic toxic effect

No toxic effects were noted in rats following ingestion of ginseng extract at a daily dose of 105-210 mg/kg for 25 weeks (Popov and Goldwag, 1973). Aphale *et al.* (1998) showed no toxicity after 90 days of ginseng administration. Chronic treatment of mice, rats, rabbits and dogs has shown very few observable signs of toxicity. No evidence of toxicity was observed in male and female beagle dogs fed ginseng extract for 90 days at daily doses up to 15 mg/kg. The study showed that there were no treatment-related changes in body weight or blood chemistry (Hess *et al.*, 1983). A long term safety investigation of ginseng product was performed in rats. Intake of the product during a 6 month period at a dose of 0.75 ml/kg did not show any unfavorable effects on integral, morphological, biochemical, and hematological parameters. In addition, two generations of rats who received ginseng product did not exhibit embryotoxic, gonadotoxic or teratogenic effects, or negative effect on growth and development of posterity (Sorokina *et al.*, 2000).

ADVERSE EFFECTS IN HUMANS

General

No significant adverse effects have been reported in ginseng clinical trials. However, several studies have observed that ginseng's side effect profile includes insomnia, headache, nausea and vomiting, diarrhea, epistaxis and skin eruption. Although the incidence of the individual symptoms was not clear, these symptoms usually occurred after inappropriate ginseng dose and its long term use (Miller, 1998; Ernst, 2002; Awang, 2002). In addition, nervousness and gastrointestinal upset have also been reported after prolonged high doses of ginseng (e.g., up to 15 g/day for 2 years) (Gillis, 1997). Clinically, "ginseng abuse syndrome" was described by Siegel, and 10% subjects experienced hypertension together with nervousness, sleeplessness, skin eruption, and morning diarrhea. Edema was also seen in five subjects (Siegel, 1979; Nocerino *et al.*, 2000). However, since this study did not differentiate between the species of ginseng used, its reliability was questioned by Mills and Bone (2000). Moreover, symptoms described in the study may also be attributed to significant caffeine intake in most of the subjects (Bucci, 2000).

Significant ginseng adverse effects can be found in limited cases. Stevens-Johnson syndrome was noted in a 27-year-old young man following the intake of 2 ginseng tablets for 3 days, resulting in

moderate infiltration of the dermis by mononuclear cells. The patient recovered completely after 30 days (Dega *et al.*, 1996; Morgan and Cupp, 2000). More seriously, agranulocytosis was induced after taking Chinese ginseng product for relief of arthritis and back pain (Faleni and Soldati, 1996). It is possible that some patients are very sensitive to ginseng administration.

Cardiovascular effects

Several clinic reports demonstrated that ginseng and its products may cause cardiovascular adverse effects. A 39-year-old Czech man who had taken various ginseng products for three years manifested hypertension, dizziness, a loud palpable 4th heart sound, and "thrusting" apical pulse. Shortness of breath and inability to concentrate were also noticed (Hammond and Whitworth, 1981; Dega *et al.*, 1996; Morgan and Cupp 2000). Another report showed that hypertension is a contraindication of ginseng administration (Carabin *et al.*, 2000). Thus, use of ginseng requires caution in patients with cardiovascular conditions, agitation, diabetes and psychosis (Sierpina, 2001). In contrast, animal studies showed that ginseng has a hypotensive effect and this effect may be related to ginseng saponin fraction. Future studies are needed to address inconsistent cardiovascular effects of ginseng.

Endocrine effects

There were several clinical reports concerning endocrine adverse effects induced by high dose of ginseng or ginseng preparations. Several of ginseng's estrogen-like effects were reported. A postmenopausal woman who had used pills and topical creams containing ginseng experienced an estrogen-like effect of mastalgia and vaginal bleeding (Greenspan, 1983). Another case reported that swelling and tenderness of the breasts were induced by ginseng in a menopausal woman (Phillipson and Anderson, 1984). Likewise, another clinical case indicated postmenopausal bleeding in a 44-year-old woman who applied a topical ginseng face cream (Hopkins *et al.*, 1986). Oshima *et al.* believed that the estrogen-like effects were not unexpected, since small quantities of estrone, estradiol, and estriol are present in ginseng root (Oshima *et al.*, 1987). However, major active constituents of ginseng are ginsenosides, which are structurally similar to steroids, such as testosterone, estrogen, and adrenocorticotropic hormone (ACTH) (Sierpina, 2001).

Based on the cases described above, pregnant, menopausal and elderly females should be advised to use ginseng prudently, and patients receiving hormonal therapy should avoid ginseng completely (Phillipson and Anderson, 1984; Miller, 1998; Bucci, 2000; Sierpina, 2001). Additionally, patients who have spontaneous nose bleeding and excessive menstrual bleeding should take ginseng prudently.

Other adverse effects

Ginseng may induce diuretic resistance in some patients (Becker *et al.*, 1996), though the possible ginseng-drug interaction mechanism is unknown. Ginseng may also interact with warfarin, an anticoagulant with a narrow therapeutic index. A case report showed that a man with a mechanical heart valve, stabilized with warfarin administration over 5 years, became destabilized following administration of a ginseng product (Janetzky and Morreale, 1997). The patient's International Normalized Ratio (INR) decreased from 3.1 to 1.5 after 2 weeks of ginseng intake. Following the discontinuation of ginseng therapy, the INR returned to 3.3 within 2 weeks. In this patient, ginseng use appeared to be associated with a significant decrease in warfarin anti-coagulation since no other changes in medicine and foods could be found to be responsible. Biochemical analysis did not detect vitamin K in ginseng (Zhang, 1980). The mechanism for this interaction has not been identified.

Although only one case report of ginseng-warfarin interaction has been reported, its impact on clinical medicine cannot be underestimated. In a number of recently published drug handbooks (e.g., Mosby's Drug Guide, 2001; Drug Interaction Facts, 2001; Handbook of Herbs and Natural Supplements, 2001) and herbal review articles published in widely read medical journals (Ang-Lee *et al.*, 2001a; Ernst, 2002), possible ginseng-warfarin interaction is discussed, indicating that the issue has received the medical community's attention. In addition, ginseng can inhibit platelet aggregation as seen *in vivo* and *in vitro* animal

experiments. Furthermore, potential bleeding by ginseng is a concern for surgical patients (Ang-Lee *et al.*, 2001a).

To date, most ginseng adverse effects are based on animal study data and individual clinical case reports. Controlled clinical studies are urgently needed to determine ginseng's potential adverse effects. Because long term, high ginseng dose use may be responsible for the reported adverse events, it is recommended that daily ginseng dose should be between 0.5-2.0 g dry root, or the equivalent extract, for short-term treatment (Ernst, 2002). Ginseng should not be used in children under the age of 2 years old.

POSSIBLE REASONS FOR THE ADVERSE

Inappropriate use or abuse

As a "king herb" in the Orient, the fame of ginseng has led to abuse or misconceptions in its use to induce adverse effects, such as "ginseng abuse syndrome". Consumers may assume that because ginseng is a natural product, it must be safe. Although the daily recommended ginseng dose is not over 2 g (Ernst, 2002), 59 g daily dose was reported to achieve behavioral stimulation (Siegel, 1979). Large ginseng dose may result in sleeplessness, depression, and nervous system disorder; long-term ginseng users may suffer from chronic insomnia, nervousness, and loose stools, among other problems (Siegel, 1979).

Variability in commercial preparations

Wide variability exists among ginseng products, and non-standardized pseudoginseng preparations are commercially available. In addition, some ginseng products were adulterated with prescription medications, including ephedrine or pseudoephedrine (Phillipson and Anderson, 1984; Faleni and Soldati, 1996).

Cui *et al.* (1994) examined 50 commercial ginseng products sold in eleven countries. Each preparation was blindly analyzed in triplicate. In 44 of these preparations the concentration of ginsenosides varied from 1.9% to 9.0% (w/w). The ginsenoside concentration in several commercial products was very low. Surprisingly, six products from three different countries (U.S., U.K., and Sweden) did not contain any ginsenosides. Another report showed that among 25 ginseng products, ginsenoside concentration varied by 15- and 36-fold, respectively. Ginseng preparations that listed specific concentrations of active ingredients contained as little as 11% and as much as 328% of the labeled concentration (Harkey *et al.*, 2001; Ang-Lee *et al.*, 2001b). This variability may lead to wide range of pharmacological activities or adverse effects. Thus, standardization of ginseng products should be a primary focus for quality assurance (Harkey *et al.*, 2001).

Different ginseng species

There are up to six recognized species of the genus *Panax*, depending on the particular botanical authority. Most botanists currently recognize three medicinal species, i.e., *Panax ginseng* (Chinese or Korean ginseng), *Panax quinquefolium* (American ginseng), and *Panax japonicus* (Japanese ginseng) (Phillipson and Anderson, 1984; Awang, 1991; Attele 1999). Chemical analysis results indicate that there are various components in different ginseng species, and each ginseng species has its own distinct ginsenoside profile. Even within a single species, the length of growth, cultivation conditions (such as soil, temperature, moisture), and harvest season affect the make up of ginsenoside contents (Liu and Xiao, 1992; Yuan *et al.*, 2002). Siberian ginseng, on the other hand, is distinct from *Panax ginseng*, and does not contain any ginsenosides. Rather, its active constituents are eleutherosides, which are glycosides with aglycons and chemically related to aridac glycosides, such as digoxin.

To compare the composition of ginsenosides in different ginseng samples, our laboratory measured six ginsenosides of Wisconsin-cultivated and Illinois-cultivated American ginseng by using high performance liquid chromatography (HPLC) analysis. Our data showed remarkable variability in these specimens, in terms of ginsenoside profile and total ginsenoside concentration. In addition, the length of cultivation also influenced content of ginsenosides (Yuan *et al.*, 2001; Yuan *et al.*, 2002). Furthermore, distribution of ginsenosides varies between different parts of the ginseng plant in the same species (Zhang *et al.*, 1980, Xie *et al.*, 2002a). The multiformity of ginseng species and variability of ginsenoside concentrations among different

species may also contribute to variable pharmacological effects and adverse effects.

Ginseng-drug interactions

Co-administration of ginseng and prescription medications may cause adverse herb-drug interactions (Windrum *et al.*, 2000; Ang-Lee *et al.*, 2001a). Ginseng may interact with a number of medications, such as warfarin, digoxin and vitamin C, possibly leading to adverse effects. It is suggested that concomitant use of ginseng with warfarin, heparin, aspirin, and NSAIDs should be avoided (Miller, 1998; Vaes and Chyka, 2000).

In addition to possible ginseng-warfarin interactions discussed earlier, another potential adverse interaction exists between ginseng and digoxin (McRae, 1996). A 74-year-old male patient taking a constant dose of digoxin for many years was found to have an elevated serum digoxin level. Common causes of elevated serum digoxin were ruled out, yet the patient's digoxin level remained high. The patient revealed that he was taking Siberian ginseng. Soon after he stopped taking Siberian ginseng, his serum digoxin returned to an acceptable level and digoxin therapy resumed. The patient resumed taking Siberian ginseng several months later and digoxin level rose again. Digoxin therapy was maintained at a constant daily dose while the ginseng was stopped once more, and the serum digoxin levels again returned to the therapeutic range. Though it is still unclear why Siberian ginseng changed digoxin level, physicians should be aware the drug interactions may exist between Siberian ginseng and digoxin.

Not all ginseng-drug interactions are detrimental. A report indicated that ginseng saponins at 0.25-1.0 mg/ml concentrations significantly protected against oxidation of low-density lipoprotein *in vitro*. The presence of vitamin C (1-10 mM) markedly enhanced the protective effects of ginseng (Li *et al.*, 2000).

SUMMARY

Herbal medications play an important role in our daily healthcare maintenance. Ginseng is one of the most commonly used herbs in China, Japan, and Korea, as well as in the United States. To minimize possible adverse effects of ginseng, consumers should be advised to use it appropriately, and the herbal industry has a responsibility to provide standardized ginseng preparations. Future investigations are needed to understand both the beneficial and adverse effects of ginseng, and their underlining mechanism of actions.

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