Review article

Review of cases of patient risk associated with ginseng abuse and misuse

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A B S T R A C T

Ginseng has long been used as a functional food or therapeutic supplement and it is empirically known to be safe and nontoxic. During recent decades, a number of in vitro and in vivo experiments, as well as human studies have been conducted to prove the safety of various types of ginseng samples and their components. Clinical trials, case reports, and in vitro and in vivo research articles addressing the safety, toxicity, and other adverse events of ginseng application were selected and reviewed. Patient risks associated with ginseng abuse and misuse such as affective disorder, allergy, cardiovascular and renal toxicity, genital organ bleeding, gynecomastia, hepatotoxicity, hypertension, reproductive toxicity, and anticoagulant-ginseng interaction were reviewed and summarized. There are some cases of patient risk associated with ginseng abuse and misuse depending on patients' conditions although further investigation in more cases is required to clarify these issues.

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1. Introduction

Ginseng has been used as a tonic and panacea in Asian countries for a long time and also as a functional food or therapeutic supplement in Western countries in recent times [1–7]. During the past few decades, a number of in vitro and in vivo experiments, as well as human studies have been conducted to prove the safety of various types of ginseng and their components.

In animals, toxic episodes of ginseng components or preparations have been reported on several occasions [8–11], although no short term or long term toxicities were observed in other experiments [12–15].

In humans, Panax ginseng is associated with mild toxicity and few adverse events have been reported. Siegel [16] described the unfavorable symptoms of ginseng based on the 2-yr follow up of 133 patients with ginseng ingestion: morning diarrhea (35%), skin eruption (25%), nervousness (25%), sleeplessness (20%), hypertension (17%), edema, decreased appetite, depression, and hypotension (∼10%). The adverse events have been associated with high doses and long-term usage [17]. The toxicity assessment of ginseng preparations in human studies suggested that a relatively low frequency of toxic incidence has been associated with ginseng application although ginseng is not without capabilities of toxicity [18]. In addition, studies based on the systematic literature analysis suggest that P. ginseng is infrequently related with toxic side effects or interactions with prescription drugs [19–21]. Overall, it is assumed that ginseng is a safe and nontoxic material although the safety issues still remain to be elucidated.

However, there is some evidence of patient risk associated with ginseng abuse and thus case reports and research articles addressing the safety issues of ginseng were collected and described in this review.

2. Affective disorder

A manic episode by ginseng intake was observed in a 56-yr-old woman with previous affective disorder. Symptoms was wiped out quickly with low doses of neuroleptics and benzodiazepines after quitting ginseng preparation [22]. Similarly, a manic symptom was developed in a 26-yr-old healthy individual with no history of psychiatric illness after consumption of Chinese ginseng capsule for 2 mo [23].

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3. Allergy

Anaphylaxis is a serious allergic response that has fast onset and may result in death. It is typically characterized by a number of symptoms including an itchy rash, throat swelling, and low blood pressure. Common causes include insect bites/stings, foods, and medications [24]. Numerous research results suggest that various types of ginseng and its components can efficiently prevent or inhibit the experimentally-induced allergic reactions [25–28] and the symptoms of atopic [29] and allergic rhinitis patients [30].

However, several case reports that ginseng is able to cause allergic reactions in human have also been described. In a case report of possible anaphylactic reaction to ginseng, a 20-yr-old male patient was exposed to Asian ginseng syrup by consumption, and developed respiratory allergy, erythematous papules, and angioedema in the body and low blood pressure [31]. Another case of anaphylactic reaction caused by *P. ginseng* was reported in a 29-yr-old female patient, who had been working in a herbal market for the past 26 mo and admitted to the emergency for respiratory distress symptom. The patient respond positively to a bronchial provocation and to a skin-prick test with ginseng-derived proteins. This confirmed that the asthma was consequent to the exposure to Korean ginseng dust and was induced via non-immunoglobulin (Ig) E mechanism [32]. Similarly, in a 44-yr-old man, open oral challenge with Korean ginseng extract induced the anaphylactic reaction by the IgE-independent activation of basophil and mast cell [33].

A 34-yr-old woman who was working at a Korean ginseng wholesale market developed recurrent dyspnea and nasal symptoms. Skin prick test and elevated serum anti-Korean ginseng specific IgE level showed that Korean ginseng is able to induce occupational asthma in an individual exposed to dried ginseng and ginseng dust for long periods [34].

Thus, it is probable that ginseng may cause an anaphylactic reaction via the IgE-dependent or independent manners in a certain type of individuals who might be predisposed or sensitized in advance to ginseng, although it is not widely observed.

4. Cardiovascular and renal toxicity

Long QT syndrome is a hereditary or acquired heart disorder characterized by a prolongation of the QT interval on electrocardiograms and a predisposition to ventricular tachyarrhythmias, which may lead to syncope, seizures, cardiac arrest, or sudden death. Application of certain medications causes QT prolongation in some individuals [35].

Regarding this issue, in a prospective, randomized, double-blind, placebo-controlled study, thirty subjects were randomly grouped to receive 28 d of treatment with either *P. ginseng* extract 200 mg or placebo. Subsequent electrocardiogram were recorded following test drug consumption at 50 min, 2 h, and 5 h on Day 1 and Day 28. Blood pressures were measured with each electrocardiogram. Ginseng extract, at daily doses of 200 mg, prolongs the QTc interval and reduces diastolic blood pressure 2 h after consumption in healthy adults on the 1st d of treatment. However, the observed effects are not seemed to be clinically relevant [36]. Another case was reported that a 43-yr-old healthy woman patient without cardiovascular risk factors who developed prolonged QT with subsequent *torsades de pointes* during periods in which she was abusing *P. ginseng* on the daily basis for 6 mo [37]. In addition, an atrial fibrillation (AF) with slow ventricular rate developed after taking Asian ginseng for 1 wk in 83-yr-old woman with old chronic renal disease [38]. However, these are the very individual reactions based on a specific condition of the one who suffers it. Thus, caution is needed for patients showing idiosyncrasy toward certain drugs or functional foods.

In experiments with isolated rat aorta and primary vascular smooth muscle cells that evaluate the effects of Rg3 on the vascular contractility and its structure, a normally unattainable, high dose of Rg3 induced irreversible damage of agonist-mediated vascular contractility via blocking the calcium ion influx through L-type calcium channel. In addition, functional abnormalities and remodeling of vascular smooth muscle were also observed by the repeated intravenous application of high dose (20 mg/kg, 4 wk) of Rg3 [9].

It is known that kidney dysfunction increases the risk of death and cardiovascular disease [39]. In searching for the link between ginseng intake and cardiovascular adverse event in renal disease, a case was reported that an 83-year-old woman with chronic renal insufficiency developed atrial fibrillation with bradycardia after ingesting ginseng for 1 wk [38]. In addition, scrutinizing the effects of long-term use of ginseng on blood pressure and renal function, another randomized, placebo-controlled, double-blinded, cross-over trial in 52 hypertensive individuals was performed. Twenty-four h blood pressure and concentration of serum cystatin C were measured after 12 wk of American ginseng consumption. The concentration of cystatin C is primarily used as an index of renal function. Recently, its possible application in expecting new-onset or deteriorating cardiovascular disease has been explored. The data suggested that long-term ginseng ingestion does not cause any influences on 24-h blood pressure and kidney function in hypertensive individuals [40].

5. Gynecomastia and genital organ bleeding

It has been repeatedly noted that *P. ginseng* is able to exert estrogen-like actions, because ginsenosides, the major components of ginseng, have structural similarity with the female sex hormone, estradiol [41]. Thus, ginseng has been used as an alternative medicine for treating postmenopausal symptoms although its effects are still controversial [42–44]. This might lead physicians to suspect the ginseng-induced gynecomastia in a man who has ingested ginseng for a long period. Since the first report of the gynecomastia associated with ginseng use [45], another case has been reported. A 12-yr-old boy was diagnosed with bilateral enlargement of the breasts with tenderness in the right breast, which was noticed after consumption of red ginseng extract daily for 1 mo. After discontinuation of this, there was no further progress in the growth of masses and in the development of pain when his right breast was pressed [46].

A 39-yr-old woman complained of menometrorrhagia. She had been using oral ginseng powder (1000–1500 mg/d) and, at the same time, ginseng cosmetics for 7 mo. By examining the clinical progress of this patient, the authors assumed that the menometrorrhagia is due to the misuse of ginseng although this could be coincidental [47]. Similar case of uterine bleeding episode was reported with the consumption of ginseng-containing preparation [48].

Regarding phytoestrogen activity of ginseng, there are several lines of evidence indicating that ginseng activates estrogen receptors. For instance, ginsenosides activate estrogen receptors in a ligand-independent manner [49,50]. Korean Red Ginseng extract activates estrogen receptor *in vitro* [51]. However, these effects are not compatible with the observation that ginseng extract did not affect the uterine weight in ovariectomized animals [51,52]. In addition, in a human endometrial adenocarcinoma cell line, Ishikawa, which contains an estrogen sensitive-alkaline phosphatase enzyme, no estrogen-like action was observed by stimulation with maximum concentration (25 μg/mL) of ginseng extract [53]. Thus,

might it not be asserted that the ginseng-related bleeding episodes and gynecomastia is due to the estrogenic activity of ginseng? Further investigation in more cases is required to clarify these issues.

6. Hepatotoxicity

A case study reported that a 26-yr-old male leukemia patient taking the antileukemia drug imatinib 400 mg/d for 7 yr without adverse effects consumed ginseng energy drinks at the same time for 3 mo and then suffered from right upper abdominal pain. After liver biopsy, it turned out to be acute lobular hepatitis. The author claims that the late onset of imatinib-induced hepatotoxicity is not probable since severe imatinib-induced hepatotoxicity is rather uncommon and it usually takes place within 1–2 years after initiation of therapy [80,81]. And thus, the hepatotoxicity is due to the interaction between ginseng and imatinib in which ginseng inhibits CYP3A4, the primary enzyme involved in the metabolism of imatinib, thereby it causes rise in concentration of imatinib to the toxic level [54].

However, it has been suggested that effects of ginseng on drug metabolizing enzymes are diverse. In human studies, long-term (28 d) treatment of ginseng capsule (500 mg, twice daily) induced the activity of CYP3A in liver and intestine [55]. In another human study, induction of CYP3A activity was not observed by treatment of ginseng extract for 14 d, 100 mg, twice daily although low concentration ginseng activates CYP4A4 *in vitro* with human liver microsomes [56]. In addition, ginseng extract induced expression of CYP3A4 in human primary hepatocyte and increased CYP3A4-mediated luciferase activity in HepG2 cells expressing luciferase reporter gene with CYP3A4 promotor [57]. By contrast, the *in vitro* study showed that ginseng is capable of inhibiting CYP2C9- and CYP3A4-mediated metabolic reactions in human liver microsomes [58]. It was also reported that imatinib is a substrate of CYP2C8 and CYP3A4 and imatinib is a potent inhibitor of CYP3A4 as well *in vitro* [59].

As a result, more cases are needed to support that notion that ginseng increases markedly the level of plasma concentration of imatinib which is able to cause severe hepatotoxicity. Thus, these notions may not be compatible with the author's claim that the imatinib–ginseng interaction is responsible for the hepatotoxicity of an individual who took imatinib and ginseng simultaneously for a long time.

7. Hypertension

A case study reported that a 64-yr-old male who had never suffered hypertension taking 500 mg of the *P. ginseng* preparation Ginseng Forte-Dietisa for 13 d experienced a transient ischemic attack (amaurosis fugax) secondary to hypertensive crisis (195/95 mmHg). One wk after quitting the ginseng product, the blood pressure was restored to its previous level (< 140/90 mmHg). The authors claimed for the first time that the consumption of Korean *P. ginseng* is related to the transient ischemic attack manifesting as amaurosis fugax by causing the hypertensive crisis [79], which is rather inconclusive. Instead, more direct evidence such as pharmacokinetic/pharmacodynamic profile is required to confirm the ginseng-induced amaurosis fugax although there is a certain temporal coincidence between ginseng intake and changes in blood pressure.

8. Photohemolysis

Significant phototoxicity by ginseng extract was observed in red blood cells when tested by photohemolysis reaction *in vitro* [60].

9. Reproduction toxicity

The safety issue of ginseng intake during pregnancy has been always controversial and needs to be resolved. Experiments were performed to test the possible toxic influence of ginseng and its components on the embryogenesis and fetal development of mouse and rat. Korean Red Ginseng extract which was orally administered to mice from 2 wk prior to mating to gestational Day 18 did not cause any significant developmental toxicity up to 2,000 mg/kg/d, which is approximately 200 times clinical doses, although the incidence of supernumerary ribs increased at the dose of 200 mg/kg/d [14].

By contrast, in the experiments with whole embryo cultures, high concentrations of ginsenoside Rg1 and Rb1 were reported to cause teratogenicity in rat and mouse, and Re in rat. Rats are more sensitive than mice to the embryonic toxicity of ginsenoside Rg1 [11,61,62]. In a separate experiment, growth of the hind- and midbrains and the caudal neural tube was significantly increased by ginsenoside Rg1, although overall morphological changes in cultured rat embryo were not observed [10].

However, these observations are challenged by the notion that the experiments were performed with animal embryos and based on exposure to isolated ginsenosides at much higher levels than attainable through usual intake in humans [63]. In addition, according to the reports that systematically analyze the effects of ginseng on reproduction, no side effects are associated with ginseng used during pregnancy and some androgenic effects reported in the literature are due to an adulterant [63]. Nevertheless, many commercial ginseng products contain those three ginsenosides at relatively high levels and, when extrapolating from the results of animal studies to humans, ginseng intake might cause weight loss, as well as mental and behavior disorders of newborns.

Surprisingly, a study showed that about 15% of women consume ginseng during pregnancy and they assume that ginseng would be beneficial for the fetus and pregnancy [64]. In the survey to study characteristics of women using herbal drugs and the possible influence of use or abuse in early pregnancy on pregnancy outcome, ginseng is one of the most frequently used herbal medicine and no notable abnormalities were observed with the consumption of ginseng in terms of premature delivery, number of newborns, weight of infants, malformations, and Apgar score [65]. Nevertheless, ingestion of ginseng and its products should be avoided during the first trimester of pregnancy and lactation periods.

10. Anticoagulant–ginseng interaction

According to Natural Medicines Comprehensive Database, nearly 180 dietary supplements and medicinal herbs are likely to interact with warfarin and ginseng is one of them [66,67]. Warfarin, a narrow margin safety anticoagulant is usually used in the prevention of thrombosis and thromboembolism. These interactions may enhance or reduce warfarin's anticoagulation effect [68–70]. Studies reviewing the extensive literature regarding the safety and pharmacology of ginseng suggest that ginseng usually tends to cause bleeding [71]. This could be supported by the facts that various types of ginseng inhibit platelet aggregation and prolong blood coagulation time in *in vitro* and experimental animal [72–74]. Thus, it may enhance the anticoagulant effects of warfarin.

Separate studies have been performed to understand the effect of various types of ginseng in thrombosis and their interactions with standard anticoagulant drugs in different clinical settings. In a reported case, ginseng was able to inhibit the anticoagulant action of warfarin significantly [75]. In the randomized, double-blind, placebo-controlled trial with a total of 20 healthy patients, American ginseng significantly reduced the peak international

Table 1
Patient risks associated with ginseng abuse and misuse

Adverse effects	Samples	Patients	Types of reports	Refs
Acute lobular hepatitis	Ginseng energy drinks	26-yr-old male leukemia patient	Case report	[54]
Allergy	Asian ginseng syrup.	20-yr-old male patient	Case report	[31]
Allergy	Panax ginseng	29-yr-old female patient	Case report	[32]
Allergy	Korean ginseng extract	44-yr-old man	Case report	[33]
Allergy	Korean ginseng	34-yr-old woman	Case report	[34]
Atrial fibrillation with bradycardia	Asian ginseng	83-yr-old woman with chronic renal insufficiency	Case report	[38]
Gynecomastia	Red ginseng extract	12-yr-old boy	Case report	[46]
Hypertensive crisis	Ginseng Forte-Dietisa	64-yr-old male who had never suffered hypertension	Case report	[79]
Increase in QTc interval and Reduction of diastolic pressure	P. ginseng extract	Total 30 healthy adults	Clinical trial	[36]
Long QT and torsades de pointes	Large amounts of ginseng drink	43-yr-old healthy woman	Case report	[37]
Manic episode	Ginseng root extract	56-yr-old woman with previous affective disorder	Case report	[22]
Manic episode	Chinese red ginseng	26-yr-old healthy individual with no history of psychiatric illness	Case report	[23]
Reduction of warfarin action	American ginseng	20 healthy individuals	Clinical trial	[76]
Uterine bleeding	Ginseng cosmetics and ginseng capsules	39-yr-old woman	Case report	[47]
Uterine bleeding	Pharmaton Complex	48-yr-old woman	Case report	[48]

normalized ratio (INR) and plasma warfarin concentration and thus inhibited warfarin's anticoagulant activity [76].

In a prospective, double-blind, randomized, two-period cross-over study, 25 patients with cardiac valve replacement under warfarin therapy were treated with either Korean Red Ginseng or placebo and then INR and warfarin concentrations were analyzed in the 3rd wk and 6th wk of each study period. Results showed that application of Korean Red Ginseng did not affect the mean INR changes compared with placebo [77]. Similarly, in the separate study with ischemic stroke patient ginseng water extract did not influence on the action of warfarin [78]. These variations may come from the types of ginseng and clinical settings. More studies are required to assess the clinical significance of these potential interactions.

11. Conclusion

Patient risks associated with ginseng abuse and misuse such as affective disorder, allergy, cardiovascular and renal toxicity, genital organ bleeding, gynecomastia, hepatotoxicity, hypertension, reproductive toxicity, and anticoagulant—ginseng interaction were reviewed and summarized. Further investigation in more cases is required to clarify these issues (Table 1) [22,23,31—34,36—38,46—48,54,76,79].

Conflicts of interest

All contributing authors declare no conflicts of interest.

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