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Constituents and Effects of Ginseng Leaf

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SUMMARY

Ginseng root has been used as a tonic remedy in Traditional Chinese Medicine for centuries. Modern studies have demonstrated that ginseng root has complex components and multiple pharmacological properties. The effects of ginseng leaf, however, are not well known. Recent studies show that compared to ginseng root, ginseng leaf and stem exhibit a higher content of active compositions such as ginsenosides, polysaccharides, triterpene flavonoids, volatile oil, polyacetylenic alcohols, peptides, amino acids and fatty acids. Ginseng leaf possesses multiple pharmacological effects in the central nervous, cardiovascular, growth and metabolism systems. Additionally, the leaf has anti-fatigue, anti-hyperglycemic, anti-oxidant, and anti-aged effects. In general, ginseng leaf is quite safe, but adverse effects may occur if it is abused or is of poor quality. Thus, attention must be paid to dosages, quality, and standardization of ginseng leaf products.

Key words: *Panax* ginseng; Panax *quinquefolius;* Ginseng root; Ginseng leaf; Constituents; Pharmacological activities; Adverse effects

INTRODUCTION

In botany, ginseng is a slow-growing, deciduous, perennial plant that belongs to the *Araliaceae* and *Panax* family. Ginseng is a valued herb that has been used as a tonic, restorative, and longevity remedy in Traditional Chinese medicine for over several thousand years (Chevallier, 2000). There are several species of ginseng in the world, such as *Panax ginseng* C. A. Meyer (Chinese ginseng or Korea ginseng) and *Panax puinquefolius* L. (American ginseng). Ginseng is cultivated in China, Japan, Korea and Russia, as well as in the United States and Canada. The root of ginseng is the most costly and most commonly used herb in Oriental Medicine. As a dietary supplement, ginseng is an extremely common and popular herbal medicine in the United States (Cheng, 2000).

Previous studies have demonstrated that the root of ginseng and its major active components (ginsenosides) have complex and multiple pharmacological actions (Attele *et al*, 1999). The root of ginseng is well known in Chinese herbal medicine for its ability to increase stamina, vitality, health, and longevity (Sun *et al*., 1992; Gillis, 1997; Li *et al*., 1999; Keum, *et al.*, 2000; Kaufman *et al.*, 2002; Kim *et al.*, 2002). The components and pharmacological properties of ginseng leaf, on the other hand, are not completely understood. More interestingly, reports indicate that the content of active compositions in the leaf is higher than in the root (Li *et al*., 1996). However, in comparison to the root, the leaf is almost completely neglected in commercial terms, although there is considerable potential for its exploitation (Lim *et al*., 1999). Due to these reasons, the present review will focus on the constituents, especially the pharmacological properties, of ginseng leaf in order to demonstrate its possible application in medicine.

CONSTITUENTS

Based on previous reports, the leaf of ginseng contains a number of important biological active

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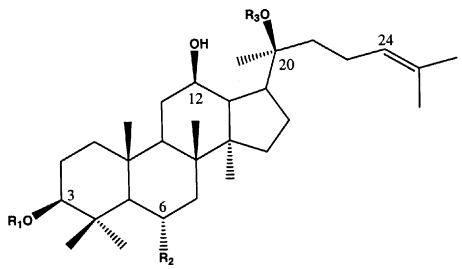
constituents (Hou, 1977; Yip *et al.*, 1985). These include ginsenosides, polysaccharides, triterpene flavonoids, volatile oil, polyacetylenic alcohols, peptides, amino acids and fatty acids (Zhonghua Bencao Editor, 1996). Most pharmacological actions of ginseng root, leaf and stem are attributed to the presence of ginsenosides (Huang, 1999). More than thirty ginsenosides have been isolated and identified (Attele *et al*., 1999), and novel structures continue to be reported, particularly from *Panax quinquefolius*, *Panax ginseng* and *Panax japonicus* (Attele *et al.*, 1999; Yang *et al.*, 2000; Dou *et al.*, 2001; Ming *et al.*, 2002). Figure 1 illustrates the structures of major ginsenosides in the ginseng leaf. Studies have shown that the ginsensonide content in the leaf is not only higher in total, but also distinct, compared to the root (Xie *et al.*, 2004). Evidence exists that there is also significant variation between major ginsenosides in the leaf itself (Li *et al.*, 1996; Li *et al.*, 2002; Jackson *et al.*, 2003, Assinewe *et al.*, 2003). Among the six major ginsenosides, Re and Rd each accounted for 30-40% of the total ginsenosides (Li *et al.*, 1996; Xie *et al.*, 2004). Thus, the leaf could be a valuable source of the ginsenosides Re, Rd, and Rb2 (Jackson *et al.*, 2003). It is worth mentioning that seasonal fluctuations, geographical differences and length of cultivation account for the variations of ginsenoside content of the leaf.



Ginsenosides	R1	R2	R3
Rb1	Glc-^{2}Glc-	H-	Glc-^{6}Glc-
Rb2	Glc-^{2}Glc-	H-	Ara(p)-^{6}Glc-
Rc	Glc-^{2}Glc-	H-	Ara(f)-^{6}Glc-
Rd	Glc-^{2}Glc-	H-	Glc-
Re	H-	Rha-^{2}Glc-O-	Glc-
Rf	H-	Rha-^{2}Glc-O-	H-
Rg1	H-	Glc-O-	Glc-

Fig. 1. Structures of major ginsenosides in ginseng leaf.

PHARMACOLOGICAL ACTIVITIES

Previous studies have demonstrated that the ginseng leaf possesses multifaceted pharmacological actions on the central nervous system (CNS), cardiovascular system, growth and metabolism system, and immune system (Saito *et al.*, 1973; Wang *et al.*, 1980; Wang *et al.*, 1983). It is also known that the stem and leaf of ginseng have anti-fatigue, anti-hyperglycemic, anti-oxidant, anti-tumor, and anti-aged activities.

Effects on the CNS

An early study showed that *Panax ginseng* leaf extract appeared in CNS-depression and neuroleptic properties in mice (Saito *et al.*, 1973). Ginseng leaf extract produced CNS-depression as revealed by its effects on reduction of spontaneous and exploratory movements and potentiation of hypnotic actions of hexobarbital. Analgesic and anticonvulsant activities were also confirmed in this study. Moreover, the extract inhibited the conditioned avoidance response in the pole climbing test.

The effects of stem-leaf saponins from Chinese ginseng (*Panax ginseng*) on memory, learning and biogenic monoamines of the brain were investigated in rats (Wang *et al.*, 1995). Results showed that ginseng root saponins (50 mg/kg x 7 days, ig.) facilitated the learning and memory of normal male rats, while the effects of ginseng stem-leaf saponins on antielectroconvulsive shock-induced impairment of memory consolidation was more intense. Also, both stem-leaf and root saponins raised the levels of biogenic monoamines significantly in the normal rat's brain. In another study, the effects of ginseng stem-leaf saponins on learning and memory of one-way avoidance were evaluated in shuttle-box rats (Ma *et al.*, 1991). The data indicated that ginseng stem-leaf saponins (10, 30, and 60 mg/kg) facilitated the acquisition of learning and memory in rats and improved the scopolamine and cycloheximide amnesia. However, another study showed that, compared to ginseng root, the extract from the overground part of Chinese ginseng had a weaker effect or no effect at all (Petkov *et al.*, 1992). Recent research also showed that Siberian ginseng leaf extract possesses anti-fatigue, anti-stress, anti-

depressive effects and exhibited CNS activity (Deyama *et al*., 2001).

Effects on cardiovascular activities

Ginseng stem and leaf extracts have been found to possess preservative effects on the cardiovascular and vascular system in animal experiments, especially protective effects on myocardial ischemia. Results of several studies exhibited that ginseng leaf extract protected myocardial cells from ischemia in dogs (Sui *et al*., 2001). Treated with American ginseng leaf extract (10, 20 mg/kg, iv.) in anaesthetized open-chest dogs, the myocardial infarct size, the activity of serum CK, LDH, and the contents of serum FFGA and LPO decreased, whereas the activity of serum SOD and GSH-Px increased markedly. Simultaneously, myocardial blood flow was increased and coronary vascular resistance decreased significantly. They concluded that the extract has protective effects on myocardial ischemia by modifying metabolic dysfunction of FFA, inhibiting oxygen free radical mediated peroxidation of membrane lipids, enhancing endogenous antioxidase activity and increasing myocardial blood supply.

Another study clearly demonstrated that Chinese ginseng stem-leaf extracts (120 mg/kg for 90 min) have beneficial effects on preservation of cardiac function as well as coronary vascular function after cold storage for 12 hours in isolated rat heart (Zheng *et al*., 1999). The experiments have shown that the extract has a remarkable influence on coronary artery dilation and an increased effect on coronary flow in response to endothelial-dependent vasodilator (Ach). Ginseng stem-leaf extracts protected the coronary endothelium and prevented coronary vascular dysfunction induced by reperfusion injury after hypothermic heart preservation. They observed that the extract not only protected the coronary endothelium, but also attenuated reperfusion damage of vascular smooth muscle cells.

In addition, American ginseng stem-leaf saponins can antagonize the effects of norepinephrine, potassium chloride, and calcium chloride on the isolated aortic strips in rabbits (Guan *et al*., 1996). This study showed that the saponins inhibited intracellular and extracellular Ca^{2+}-dependent contractions induced by NE in the aortic strips of rabbits. Similar results obtained from another study revealed that American ginseng saponins (0.03-3 mg/ml) inhibited the contractility of papillary muscle in guinea pigs (Chen *et al*., 1994). Clinical trials also showed that a Chinese medicine, Shenshao Tongguan Pian, containing ginseng stem-leaf extract positively treated angina pectoris of coronary heart disease (CHD) (Hu *et al*., 1990). The authors carried out a randomized double-blind trial on 565 cases of CHD from 1982 to 1988. The total effective rates of treating angina pectoris were 94.7% and 67.0% in the trial and control groups, respectively. Their animal experiments also indicated that the medicine had more potent action on the cardiovascular system, as seen in dilation of coronary arteries, promotion of coronary perfusion flow, lowering oxygen consumption of heart muscle, resisting the coronary spasm, anoxia and ischemia of heart muscle elicited by pituitrin, and prolongation of survival time in mice under anoxic state.

Interestingly, reports revealed ginseng stem-leaf extract affects atrial natriuretic peptide gene expression in older rats (Hong, 1991; Hong *et al*., 1992). This study displayed that both ginseng stem-leaf and root extracts (50 mg/kg body Wt, once a day for 7 days) increased the ANP-mRNA content of male and female rats at 2-3 months. However, the ANP gene expression declined during ontogenic aging development and ginsenosides possessed anti-aging effects in the heart endocrineous function.

Effects on growth and metabolism

Wang *et al* (1982) conducted a few studies on the pharmacological effects of ginsenosides from Chinese ginseng stem-leaf. When ginsenosides were given to young mice or rats (po. or ip.), a marked increase of body weight in the animals was noted. They also observed that ginsenosides sped up the growth of young pigs, and significantly the protein and RNA contents of muscles and liver in rats increased significantly. They suggested that the promotion of animal growth by ginsenosides may be due to its direct influence on syntheses of RNA and protein.

Another research reported the effect of aerobic exercise and its combination with ginsenosides from ginseng stem-leaf on lipid metabolism in

hyperlipidemia mice. This experiment indicated that aerobic exercise could lower serum lipid to some extent but could not satisfactorily regulate lipid metabolism. When combined with ginsenosides, aerobic exercise could better lower serum lipid, regulate lipid metabolism, promote antioxidation, and enhance immune activity (Yang *et al*., 1999). In the other study, rise of total lipid, cholesterol and triglyceride levels in rabbits were markedly inhibited by oral administration of ginsenosides from stems and leaves at a daily dose of 60 mg/kg body Wt. In this experiment, the inhibitory rates were 66.2%, 92.8%, and 58.1 %, respectively (Wen *et al.*, 1996).

Anti-hyperglycemic effects

Previous studies have shown that both Chinese and American ginseng root possess anti-hyperglycemic actions (Sotaniemi *et al*., 1995; Vuksan *et al*., 2000; Vuksan *et al*., 2001; Chung *et al*., 2001). Recently, we have demonstrated that ginseng berry (or fruit) extract, which has a distinct ginsenoside profile compared to that of the root, has the ability to reduce hyperglycemia and body weight both in C57BL/6J *ob/ob* mice (Attele *et al*., 2002; Xie *et al*., 2002-a) and C57BL/Ks *db/db* mice (Xie *et al*., 2002-b). However, there were only few reports that suggested ginseng leaf extract contributed to this anti-diabetic effect (Molokovskii *et al*., 1989; Broadhurst *et al*., 2000; Xie *et al*., 2004). One study exhibited that ginseng leaf and root tinctures have anti-hyperglycemic effects in mice and rats with alloxan diabetes (Molokovskii *et al*., 1989). The authors discussed mechanisms of anti-diabetic, insulinotropic and hypoglucagonemic action of the effective plant pharmaceuticals and the prospects of their use in multimodality therapy of diabetes of type 1. The other report showed that ginseng root and leaf extracts increased the basal content of insulin in blood and the glucose-dependent secretion of this hormone (Davydov *et al*., 1990).

Recently, our group analyzed the active constituents of American ginseng leaf by using high performance liquid chromatography (HPLC), and evaluated its hypoglycemic properties in diabetic *ob/ob* mice (Xie *et al*., 2003). The results indicated that American ginseng leaf extract administration (ip. 50 or/and 150 mg/kg body Wt) significantly reduced high blood glucose levels. Intraperitoneal glucose tolerance test data showed that leaf extract at doses of 150 mg/kg and 50 mg/kg in both groups had significant improvement in glucose disposal on Day 12 compared to vehicle group. On the other hand, ginseng leaf extract decreased body weight in *ob/ob* mice. We suggest that the anti-hyperglycemic activity of the leaf extract may prove to be beneficial in the prevention and management of type 2 diabetes. We conclude that the American ginseng leaf extract, with its high ginsenoside yield, has promising potential to be an inexpensive alternative compared to the root in ginseng treatment of diabetes mellitus.

Anti-oxidant activities

Several studies indicated that American ginseng root possesses antioxidant properties (Li *et al*., 1996; Li *et al*., 1999; Kitts *et al*., 2000; Dou *et al*., 2001; Deyama *et al*., 2001). Recently, we have demonstrated that American ginseng berry extract also has antioxidant activity (Shao *et al*., 2003). When the effects of ginseng berry and ginseng root were compared in cardiomyocytes exposed to antimycin A, we observed that American ginseng berry extract conferred stronger antioxidant protection compared to the American ginseng root extract. Our results suggested that American ginseng berry extract is a potent antioxidant that protects cardiomyocytes against oxidant-mediated injury, and this protection is partly mediated by its radical scavenging properties.

As expected, the saponin extracted from American ginseng stem-leaf (0.25-1 mg/ml) also possesses antioxidant properties in cultured cardiomyocytes of rat (Li *et al*., 1999). Their functional studies showed that the saponin concentration dependently reduced lipid peroxide levels as measured by the amount of thiobarbituric acid reactive substances formed. In conclusion, they suggested that American ginseng stem-leaf extract has antioxidant properties and that reduction of low-density lipoprotein (LDL) oxidation by the saponin may provide a protective effect against the detrimental actions of oxidized-LDL. Additionally, Rb1, Rb2 and Rb3 (30 mg/ml) extracted from *Panax ginseng* stem-leaf restored the action potentials of free radical damaged

cells to normal, indicating their antioxidant action (Jiang *et al*., 1992).

Other effects

Anti-fatigue: Like ginseng root, Chinese ginseng stem-leaf extract also possesses anti-fatigue effects (Wang *et al.*, 1983). The saponins of stems and leaves of *Panax* ginseng (SSLG) were orally administered to rats daily for 6 successive days (100 or 200 mg/kg body Wt). The results showed that SSLG prolonged swimming time significantly and inhibited the increase of blood lactic acid, as well as reduced liver and rectus femoris muscle glycogens. The study demonstrated that SSLG promoted the synthesis of protein and RNA in liver and muscle tissue, an action similar to that observed using the extract isolated from ginseng root. The authors suggested that the raising of blood lipid levels by SSLG could serve as one indication of its anti-fatigue mechanism.

Anti-ulcer effect: The root of *Panax ginseng* is a well known Chinese drug widely used clinically for the treatment of gastrointestinal disorders as well as an erythropoietic and tonic remedy (Sun *et al*., 1992). The authors also found that the crude polysaccharide fraction from the leaves showed potent anti-ulcer activity against acute gastric lesions induced by a necrotizing agent in mice.

Anti-diuretic effect: Anti-diuretic effects with dose-dependence were another pharmacological property of ginsenoside selected from *Panax ginseng* stem-leaf (Wang *et al*., 1980). The total ginsenosides of the stem-leaf caused a retention of water and Na^+, an increase of K^+ excretion, and a decrease of the ratio of urinary Na^+/K^+ in rate when given ginsenosides (12 g/kg, po. or 126 mg/kg ip.) in rats. The results are in favor of the hypothesis that the DOCA-like action of ginsenosides is the result of stimulation of the release of mineralocorticoid.

Anti-aging effects: A clinical study showed that Tongbu No.1, a traditional Chinese medicine containing ginseng leaf, has a comprehensive effect in age retardation. The study indicated that this medicine could improve various symptoms of aging, and affects regulation of immune and endocrinal function, scavenges free radicals and adjusts coli flora (Zhou *et al.*, 1999).

Inductive differentiation effect: An experiment showed ginsenosides extracted from *Panax ginseng* stem-leaf have an inductive differentiation effect on all types of acute nonlymphocytic leukemia cells in primary culture (Yi *et al.*, 1993). The authors suggested that the effect of ginsenosides might be due to the comprehensive effect of increasing intracellular cAMP and inducing interferon activity.

POTENTIAL ADVERSE EFFECTS

Ginseng maintains a strong reputation in Oriental Medicine and is considered a main herbal remedy in the East. In general, ginseng and its supplements have shown to be quite safe in both animal experiments and clinical trials (Sotaniemi *et al*., 1995; Singh *et al*., 2001). Therefore, Asian ginseng is classified as a generally safe herb along with feverfew, garlic, ginkgo, saw palmetto, St. John's wort, and valerian (Klepser and Klepser, 1999). However, ginseng, including ginseng leaf, may exhibit some adverse effects (Xie *et al*., 2002-c). Although ginseng has a well-established safety record and is considered a nontoxic herb, occasional adverse reactions occur. For example, it has been incriminated in some cases due to toxicity (Tomlinson *et al*., 2000). As with any medicine, including herbs, ginseng is not free of adverse effects. The exact incidence of these effects is unknown, but apparently minor when used appropriately (Ernst, 2002). A systematic review about adverse effects of ginseng suggested that *Panax ginseng* monopreparations are rarely associated with adverse events or drug interactions (Coon and Ernst, 2002). The adverse effects in clinical trials or toxicity in animal experiment were caused when ginseng was abused or had a quality problem (Siegel, 1979; Nocerino *et al*., 2000; Morgan and Cupp, 2000; Ang-Lee *et al.*, 2001).

Such harmful results are not surprising; as the famous adage of a Swiss doctor claims (1493-1541), "all things are poisons and there is nothing that is harmless, the dose alone decides that something is no poison." This is absolutely true for all herbal medicines, including ginseng. Anything that has a demonstrable pharmacological effect is likely to result in toxicity if used inappropriately. Excessive doses, improper preparation, erroneous substitution,

or adulteration with potent herbs, nontraditional drugs, or heavy metals, may all result in toxicity (Tomlinson *et al.*, 2000). In order to correctly exploit ginseng leaf and stem, we should address its adverse effects and toxicity in this review.

Acute toxic effects

A report showed a LD_{50} (lethal dose to 50% of the sample) of ginsenosides of *Panax ginseng* stem-leaf was 0.67±0.06 g/kg by ip. in mice. When mice were given these ginsenosides 50 g/kg by po., no death occurred in these experiments (Wang *et al.*, 1980; Wang *et al.*, 1982). Another report (Saito *et al.*, 1973) indicated that LD_{50} of crude saponin fraction and saponins of ginseng leaves were 381 mg/kg and 299 mg/kg by iv. injection, respectively. Behavioral changes were observed in lethal doses: crude saponin fraction produced extended posture with abdomen touching floors and abnormal gait a few minutes after treatment. A sedative state was seen for several minutes and approximately 10 minutes later, swimming convulsions appeared and mice died after 15-25 minutes. The data shown above was 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 collection (Gillis, 1997).

Subacute toxic effects

In the subacute toxic experiments in rats, the ginseng's leaf and stem extracts (20-80 mg/kg, ip. for 21 days) did not affect erythrocytes, leukocytes, number of thrombocytes, hemoglobin, and renal function (Wang *et al.*, 1982). There was significant increase in body weight, food consumption, and liver weight of rats in another subacute study (Wang *et al.*, 1982). Brain, heart, lungs, liver, spleen, kidneys, stomach, testises, and ovaries were normal on gross examination and histopathologically. The study concluded that when used appropriately, high quality ginseng leaf and its preparations appear to be relatively safe.

CONCLUSIONS

Ginseng has been one of the most valuable and commonly used herbs in the Far East for several thousands of years. Compared to ginseng root, ginseng leaf exhibits a higher content of active compositions, and possesses multiple pharmacological activities. The economic costs of ginseng root, however, are much higher than leaf in the market. But, in fact, the leaf has a unique composition of ginsenosides and may be the richest source of the entire plant. Exploitation of ginseng leaf could greatly reduce the costs associated with ginseng harvesting and manufacturing, and thus, present a significant treatment potential in regards to some of the most currently vexing health problems in the world.

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