

Review

Open Access

Ginseng leaf-stem: bioactive constituents and pharmacological functions

Hongwei Wang¹, Dacheng Peng² and Jingtian Xie*²

Address: ¹Section of Endocrinology, Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637, USA and ²Ben May Department for Cancer Research, Pritzker School of Medicine, University of Chicago, Chicago, Illinois 60637, USA

Email: Hongwei Wang - hwang1@medicine.bsd.uchicago.edu; Dacheng Peng - dpeng@uchicago.edu; Jingtian Xie* - jingtian.xie@gmail.com

* Corresponding author

Published: 22 October 2009

Received: 30 April 2009

Chinese Medicine 2009, 4:20 doi:10.1186/1749-8546-4-20

Accepted: 22 October 2009

This article is available from: <http://www.cmjournal.org/content/4/1/20>

© 2009 Wang et al; licensee BioMed Central Ltd.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

Ginseng root is used more often than other parts such as leaf stem although extracts from ginseng leaf-stem also contain similar active ingredients with pharmacological functions. Ginseng's leaf-stems are more readily available at a lower cost than its root. This article reviews the pharmacological effects of ginseng leaf-stem on some diseases and adverse effects due to excessive consumption. Ginseng leaf-stem extract contains numerous active ingredients, such as ginsenosides, polysaccharides, triterpenoids, flavonoids, volatile oils, polyacetylenic alcohols, peptides, amino acids and fatty acids. The extract contains larger amounts of the same active ingredients than the root. These active ingredients produce multifaceted pharmacological effects on the central nervous system, as well as on the cardiovascular, reproductive and metabolic systems. Ginseng leaf-stem extract also has anti-fatigue, anti-hyperglycemic, anti-obesity, anti-cancer, anti-oxidant and anti-aging properties. In normal use, ginseng leaf-stem extract is quite safe; adverse effects occur only when it is over dosed or is of poor quality. Extracts from ginseng root and leaf-stem have similar multifaceted pharmacological activities (for example central nervous and cardiovascular systems). In terms of costs and source availability, however, ginseng leaf-stem has advantages over its root. Further research will facilitate a wider use of ginseng leaf-stem.

Background

Ginseng is cultivated in China, Korea, Japan and Russia, as well as in the United States and Canada. Ginseng is one of the most well-known herbal medicines widely used in East Asia as a tonic, restorative and anti-aging agent in traditional Chinese medicine [1-8]. Ginseng is a slow-growing, deciduous, perennial plant of the *Araliaceae* family which includes *Panax ginseng* (*Renshen*, Chinese or Korean ginseng), *Panax japonicus* (Japanese ginseng) and *Panax quinquefolius* (*Xiyangshen*, American ginseng) [9]. Ginseng is used as a dietary supplement in the United States [10].

In Chinese medicine practice, ginseng root is the most commonly used part of the plant. It contains ginsenosides as the major bioactive components known to have complex and multiple pharmacological effects [2,11].

While ginseng leaf-stem was less studied [12], a recent report indicates that American ginseng leaf contains similar pharmacologically active ingredients more abundantly than ginseng root [13]. *Panax ginseng* leaf-stem is rich in containing several ginsenosides. Therefore, this article reviews the constituents and pharmacological profile of ginseng leaf-stem, including its chemical components,

biological activities, pharmacological properties and adverse effects.

Bioactive constituents

Ginseng leaf-stem extract contains a number of important bioactive constituents [14,15], namely ginsenosides, polysaccharides, triterpenoids and flavonoids [16]. Among other constituents, ginsenosides exert main pharmacological actions of ginseng root, leaf-stem and berry [17]. More than 30 ginsenosides have been isolated and identified [10] in *Panax quinquefolius*, *Panax ginseng* and *Panax japonicus* [11,18-20]. Ginsenoside content in the leaf of *Panax quinquefolius* is higher than in the root [21]. However, significant variations in content exist between major ginsenosides in the leaf [13,22-24]. Re and Rd are the major ginsenosides in the ginseng leaf [13,21]. Ginseng leaf-stem may be a valuable source for Re, Rd and Rb2 [23].

Seasonal fluctuations, geographical differences and age variations may affect the ginsenoside content in ginseng leaf. According to a study using solid phase extraction and high performance liquid chromatography (HPLC) on American ginseng leaf and [25], Rh1, Rg2, 20(R)-Rg2 and Rg3 accounted for 4.71% in leaf and 5.35% in berry of American. A RP-HPLC (Reversed-Phase High Performance Liquid Chromatography) study on Rh2 saponin of American ginseng leaf studied the transform ratio of 20(S)-ginsenoside Rh2 [26]. Using HPLC with UV detection at 203 nm, Shi *et al.* found that the seven major ginsenosides (Rg1, Re, Rb1, Rc, Rb2, Rb3 and Rd) were present in various parts of Chinese ginseng of various ages [27]. These results also indicate that ginsenoside content is higher in the leaf and root hair but lower in the stem than that in other parts of the plant and that the total content of ginsenosides in the leaf decreases with age [25-27].

Yan *et al.* developed a simple and reliable liquid chromatography/electron spray ionization mass spectrometry (LC-ESI/MS) assay to detect Chinese ginseng leaf-stem saponin (GLSS) in methanol and rat plasma and to construct the fingerprints of GLSS reference substances and plasma samples. Thirty-one compounds were detected in GLSS, ten of which were identified in the fingerprints of reference substances and the spiked plasma sample. Twelve compounds in GLSS, including C7, C8, C14, C15, C18, Re, C24, Rb(1), Rc, Rb(2), Rb(3) and Rd were easily absorbed and might be the metabolites of GLSS [28]. Moreover, two new compounds were separated from *Panax ginseng* leaf [29].

Pharmacological functions

Ginseng leaf-stem extracts exhibit multifaceted pharmacological actions in the central nervous system (CNS), cardiovascular system, growth-metabolism system and

immune system [30-32] (Table 1). Ginseng leaf-stem extracts also possess anti-fatigue, anti-hyperglycemic, anti-obesity, anti-cancer, anti-oxidant and anti-aging activities as described below.

Effects on the CNS

An early study revealed that ginseng leaf extract caused CNS depression and neuroleptic effects in mice [30-32]. The extract-induced CNS depression was observed along with a reduction of spontaneous and exploratory movements and the potentiation of hypnotic actions of hexobarbital. Analgesic and anticonvulsant activities were also confirmed in this study. Moreover, ginseng leaf extract inhibited conditioned avoidance response in the pole climbing test.

Effects of saponins from Chinese ginseng leaf-stem on memory, learning and biogenic monoamines of the brain were also examined in rats [33]. Results showed that ginseng root saponins improved learning and memory in normal male rats, while the effects of ginseng leaf-stem saponins on anti-electroconvulsive shock-induced impairment of memory consolidation were more intense. Both leaf-stem and root saponins raised the levels of biogenic monoamines significantly in the brains of normal rats. In another study, the effects of ginseng leaf-stem saponins on learning and memory of one-way avoidance were evaluated in shuttle-box rats [34]. The data indicated that ginseng leaf-stem saponins facilitated the acquisition of learning and memory and ameliorated scopolamine and cycloheximide amnesia. Effects of ginseng leaf extract on the CNS were also examined in various species of ginseng [35]. For example, Siberian ginseng leaf extract was found to have anti-fatigue, anti-stress and anti-depressive effects. An *In vivo* study revealed that a Chinese herbal formula consisting of ginseng leaf, namely *Jiannaoning*, improved memory function in rats with cerebral ischemia [36] and that *Jiannaoning* regulated the levels of interleukin-2, interleukin-6 and neuropeptide Y in rat brain. Moreover, ginsenosides from ginseng leaf-stem affected the level of glucocorticoid receptor (GR) in brain cytosol in heat-damaged rats [37]. Binding activities of GR in brain, lung and liver cytosols and the expression levels of GR mRNA in brain and liver cytosols were all higher in the ginsenosides-treated groups than the untreated control group. Ginsenosides reduced GR binding activity in viscera which may have induced the expression of GR mRNA. Another study [38], however, indicated that extract from the aboveground part of Chinese ginseng (including ginseng leaf-stem) had a weaker effect or no effect on the animal behavior compared to ginseng root.

Effects on cardiovascular system

Ginseng leaf extracts had preservative effects on the cardiac and vascular systems and prevented myocardial

Table 1: Major pharmacological effects of ginseng leaf-stem extracts

Pharmacological effects	Dose	Subjects	References
Central nervous system			
CNS-depression effects	--	Mice	[30-32]
Anti-electroconvulsive shock	50 mg/kg × 7 days	Rats	[33]
Improving memory	11.25 g/kg <i>Jiannaoning</i>	Rats	[36]
Cardiovascular system			
Protecting cardiac cell	20 mg/kg iv; 54,27,13.5 mg/kg	Dogs; rats	[39,40]
Preventing coronary vascular dysfunction	120 mg/kg	Rats	[41]
Antagonizing (NE, KCl, CaCl ₂) effects	0.03-3 mg/min	Rabbits; guinea pigs	[42,43]
Anti-CHD effects	--	Patients	[44]
Effects on ANP gene expression	50 mg/kg × 7 d	Rats	[45,46]
Effects on Growth and metabolism			
Increasing body weight	--	Young mice and rats	[32]
Effects on lipid metabolism	--	Hyperlipidemic mice	[47]
Regulating lipid metabolism	60 mg/kg	Rabbits	[48]
Anti-hyperglycemic effects			
Anti-diabetic effects	--	Diabetic patients	[49]
Anti-hyperglycemic effects	--	Mice, rats	[58]
Lowering blood glucose	150 mg/kg × 12 d	<i>ob/ob</i> mice	[21]
Increasing blood insulin	--	Mice; rats	[60]
Hypoglycemic activities	200 mg/kg × 12 d	<i>ob/ob</i> mice	[61]
Anti-obesity activities			
Decreasing body weight	150 mg/kg × 12 d	<i>ob/ob</i> mice	[21,61]
Anti-cancer effects			
Anti-prostate, bladder and renal cancer	--	Patients	[63]
Killing cancer cells via at least 5 pathways	--	Normal and cancer cells	[64]
Reducing apoptotic cell number	60-140 mg/kg	Mouse cells	[65]
Anti-oxidant activity			
Suppressing antioxidant enzyme activity	40-200 mg/kg	Diabetic rats	[69]
Antioxidant property in cardiac cells	0.25-1 mg/ml	Rat cultured cardiac cells	[8]
Restoring free radical-damaged cells	30 µg/ml (Rb1,2,3)	Cultured myocardiomyocytes	[72]
Other pharmacological effects			
Anti-fatigue	100/200 mg/kg	Rats	[73]
Anti-ulcer	100 mg/kg	Mice	[6]
Anti-diuretic	--	Rats	[31]
Anti-aging	--	Patients	[74]
Anti-foot-and-mouth disease	10 µg* +oil emulsion	Mice	[76]

ischemia in animal experiments [39]. In anaesthetized open-chest dogs treated with American ginseng leaf extract, the myocardial infarct size, activity of serum creatine kinase (CK), lactate dehydrogenase (LDH), the contents of serum free fatty acid (FFA) and lactoperoxidase (LPO) significantly decreased, whereas the activity of serum superoxide dismutase (SOD) and Glutathione peroxidase (GSH-Px) significantly increased. At the same time, myocardial blood flow was increased and coronary vascular resistance was decreased. The results indicate that the ginseng leaf extract protected against myocardial ischemia by modifying metabolic dysfunction of FFA, inhibiting oxygen free radical-mediated peroxidation of membrane lipids, enhancing endogenous antioxidant activity and increasing myocardial blood supply. Another study [40] confirmed that ginseng leaf-stem extract protects against acute myocardial infarction (AMI) in rats by

promoting angiogenesis in the infarcted or ischemic area of myocardium.

A previous study demonstrated that Chinese ginseng leaf-stem extracts had beneficial effects on the preservation of cardiac and coronary vascular functions after cold storage for 12 hours in isolated rat hearts. The extracts increased coronary artery dilation and coronary flow in response to an endothelial-dependent vasodilator (ACh), protected the coronary endothelium, prevented coronary vascular dysfunction induced by reperfusion injury after hypothermic heart preservation and attenuated reperfusion damage of vascular smooth muscle cells [41].

Furthermore, American ginseng leaf-stem saponins were reported to antagonize the effects of norepinephrine (NE), potassium chloride and calcium chloride on the isolated aortic strips of rabbits [42]. The saponins inhibited

intracellular and extracellular Ca²⁺-dependent contractions induced by NE in rabbit aortic strips. Another study revealed that American ginseng saponins inhibited the contractility of guinea pig papillary muscle [43]. A randomized controlled trial with double blinding indicated that *Shenshao Tongguan Piana*, a proprietary Chinese medicine formula containing ginseng leaf-stem extract, effectively treated angina pectoris in coronary heart disease (CHD) with effective rates of 94.7% and 67.0% in the treatment and control groups respectively [44].

Several studies revealed that ginseng leaf-stem extract affected atrial natriuretic peptide (ANP) gene expression in older rats [45,46] and that both ginseng leaf-stem and root extracts increased the ANP mRNA in rats. An *in vivo* study on American ginseng leaf extracts showed that the expression of vascular endothelial growth factor (VEGF) and mean micro-vessel density were higher in the ginseng leaf saponin groups than in the vehicle model group and that the expression of basic fibroblast growth factor (bFGF) was higher in the ginseng leaf saponin groups than in the vehicle model group [40], suggesting that ginseng leaf-stem extracts may protect myocardium from ischemic injury in rats with AMI by up-regulating VEGF and bFGF in myocardial cells thereby inducing angiogenesis.

Effects on growth and intermediary metabolism

Ginsenosides from Chinese ginseng leaf-stem significantly increased the protein and RNA contents of muscles and liver in rats and that ginsenosides accelerated the growth of young pigs. It was suggested that ginsenosides may have direct influence on RNA and protein synthesis [32].

Ginsenosides from ginseng leaf-stem coupled with aerobic exercise lowered serum lipid, regulated lipid metabolism, promoted antioxidation and enhanced immune activity [47]. Oral administration of ginsenosides extracted from ginseng leaf-stem significantly inhibited the rise of total lipid, cholesterol and triglyceride in rabbits [48].

Anti-hyperglycemic effects

One third of diabetic patients use dietary supplements or alternative medicines [49]. Previous studies indicated that ginseng is an important alternative medicine to treat diabetes and both Chinese and American ginseng roots had anti-hyperglycemic effect [50-53]. Ginseng berry extract reduced hyperglycemia and body weight in C57BL/6J *ob/ob* mice [54,55] and C57BL/Ks *db/db* mice [56]. Ginseng leaf-stem extracts also had this anti-diabetic effect [21,57,58]. Ginseng leaf and root extracts increased the basal content and glucose-dependent secretion of insulin in blood [59].

Active ingredients and hypoglycemic properties of American ginseng leaf were examined with high performance liquid chromatography (HPLC) in diabetic *ob/ob* mice [21]. The results indicated that American ginseng leaf extract significantly reduced blood glucose levels. Intra-peritoneal glucose tolerance test showed that the leaf extract significantly improved glucose disposal. Thus, American ginseng leaf extract, with its high ginsenoside yield, may be an inexpensive alternative to the root for diabetic treatment. Similar anti-hyperglycemic activity was observed in a study on total ginsenosides of Chinese ginseng leaf-stem [60].

Anti-obesity effect

Obesity is a serious medical disorder that may cause a myriad of health problems, such as heart disease, hypertension and adult-onset diabetes. Berry, root and leaf extracts of American and Chinese ginseng as well as total ginsenosides of Chinese ginseng leaf-stem had anti-obesity activities in animals and that American ginseng leaf extract significantly reduced body weight in adult *ob/ob* mice [21,54,56,60,61].

Anti-cancer effect

Anti-cancer effect of ginseng leaf-stem is an important pharmacological function. Anti-cancer effects of Chinese ginseng leaf extract were found after co-administration of acidic polysaccharide from Chinese ginseng leaf enhanced therapeutic effects and reduced hematopoietic complications induced by systemic chemotherapy or radiation therapy [62]. Acidic polysaccharide may be a novel and potent immunotropic agent to improve cellular immunity and an anti-cancer drug to treat urological cancer patients. Extract of Indian ginseng leaf (*Ashwagandha*) had anti-cancer activities [63]. Total saponins from *Panax ginseng* leaf-stem protected against cyclophosphamide (a commonly used anti-cancer compound)-induced genotoxicity and apoptosis in bone marrow cells and peripheral lymphocytes in mice [64]. Thus, ginseng leaf extracts can be a new source for anti-cancer drugs.

Kitts *et al.* also confirmed that ginsenoside Rh2 extracted from American ginseng leaf induced cytotoxicity in cultured leukemia THP-1 cells [65]. Flow cytometry of cells stained with annexin V-fluorescein isothiocyanate and propidium iodide showed that the Rh2 from ginseng leaf significantly increased apoptosis at a concentration that inhibited cell viability by 50% (LC₅₀). Ginsenoside (Rh2) may be the active ingredient for anti-cancer activity in ginseng leaf [65].

Anti-oxidant activities

Extracts from American ginseng root and berry possess antioxidant properties [5,13,35,66,67] and so does ginseng leaf extract. In streptozotocin-induced diabetic rats,

oral administration of wild ginseng leaf extract (WGLE) effectively suppressed lipid peroxidation in diabetic rats [68]. Similar antioxidant activities were observed in cultivated and wild Korean ginseng leaf extracts [69]. It was confirmed that water, methanol and ethanol extracts from freeze-dried leaves of wild ginseng exhibited scavenging activities towards DPPH (2,2-diphenyl-2-picrylhydrazyl hydrate), superoxide anion and hydroxyl radicals. Among various solvents used to extract wild ginseng leaves, ethanol yielded the highest DPPH, hydroxyl radical scavenging and ferrous ion chelating activity [70].

Not surprisingly, the saponin extracted from American ginseng leaf-stem (0.25-1 mg/ml) also demonstrated antioxidant properties in cultured rat cardiomyocytes [5]. Moreover, Rb1, Rb2 and Rb3 extracted from *Panax ginseng* leaf-stem restored the action potentials of free radical damaged cells [71].

Other effects

Anti-fatigue effect

Chinese ginseng leaf-stem extract had anti-fatigue effects. In rats, orally administered saponins extracted from Chinese ginseng leaf-stem significantly prolonged swimming time, inhibited the increase of blood lactic acid and reduced liver and rectus femoris muscle glycogen. Ginseng leaf-stem extract also facilitated the synthesis of protein and expression of mRNA in liver and muscle tissues [72].

Anti-ulcer effect

Panax ginseng root is used in Chinese medicine to treat gastrointestinal disorders. Research showed that the crude polysaccharide fraction from ginseng leaf exhibited potent anti-ulcer activity against acute gastric lesions in mice [3].

Anti-diuretic effect

Anti-diuresis was another pharmacological property of ginsenoside from *Panax ginseng* leaf-stem. Total ginsenosides from the leaf-stem helped retain water and Na⁺, increased K⁺ excretion and reduced the ratio of urinary Na⁺/K⁺ in rats [73].

Anti-aging effects

A clinical trial showed that *Tongbu* No.1, a proprietary Chinese medicine formula containing ginseng leaf, improved various symptoms related to aging, improved immune and endocrinal functions, scavenged free radicals and adjusted intestinal flora [74].

Inductive differentiation effect

Ginsenosides from *Panax ginseng* leaf-stem induced the differentiation of all types of acute nonlymphocytic leukemia cells in primary culture [75].

Saponins, as well as the combination of saponins and oil, significantly enhanced the immune response in mice to vaccination against foot-and-mouth disease (FMDV) [76]. Co-administered with the saponins, FMDV antigen induced a significantly higher IgG response than FMDV antigen used alone.

Potential adverse effects

Both animal experiments and clinical trials have shown that normal use of ginseng is safe [50,76]. Asian ginseng is classified as a generally safe herb along with feverfew, garlic, ginkgo, saw palmetto, St. John's wort and valerian [77]. Ginseng, including ginseng root and leaf-stem, may exhibit minor adverse effects [78]. A systematic review of adverse effects of ginseng suggested that *Panax ginseng* monopreparations are rarely associated with adverse events or drug interactions [79]. The adverse effects in clinical trials or toxic effects in animal experiments were attributed to improper use or poor quality of ginseng [80-83].

Acute toxic effects

Toxicity of ginsenosides from *Panax ginseng* leaf-stem was determined in mice. When mice were given ginsenosides per oral, no death occurred [31,32]. Another report [84] indicated that the LD₅₀ values of crude saponin fraction and saponins of ginseng leaves were 381 mg/kg and 299 mg/kg respectively.

Subacute toxic effects

Ginseng leaf-stem extracts did not affect the number of erythrocytes, leukocytes, thrombocytes, the amount of hemoglobin or renal function in subacute toxic experiments in rats [32]. Body weight, food consumption and liver weight of rats increased [32]. Brain, heart, lungs, liver, spleen, kidneys, stomach, testes and ovaries were normal on gross examination and histopathological study. These findings suggested that high quality ginseng leaf-stem and its preparations were safe in normal use.

Limitations of current research

(1) Most studies on the constituents of ginseng leaf-stem extract have been qualitative. Quantitative studies will be required. (2) Quality control of ginseng leaf-stem preparations has not been adequately assured. (3) Few randomized, double-blind, placebo-controlled clinical trials on ginseng leaf-stem extracts are available. Further laboratory and clinical studies are warranted for wider pharmaceutical use of ginseng leaf-stem.

Conclusion

Extracts from ginseng root and leaf-stem have similar multifaceted pharmacological activities (e.g. CNS and cardiovascular system). In terms of costs and source availability, ginseng leaf-stem has advantages over its root.

Further research will facilitate a wider use of ginseng leaf-stem.

Abbreviations

AMI: acute myocardial infarction; ANP: atrial natriuretic peptide; bFGF: basic fibroblast growth factor; CHD: coronary heart disease; CK: creatine kinase; CNS: central nervous system; CHD: coronary heart disease; FFA: free fatty acid; GLSS: ginseng leaf-stem saponin; GSH-Px: Glutathione peroxidase; GR: glucocorticoid receptor; HPLC: high performance liquid chromatography; LC/ESI-MS: liquid chromatography/electron spray ionization mass spectrometry; LD₅₀: lethal dose to 50% of the sample; LDH: lactate dehydrogenase; LDL: low-density lipoprotein; LPO: lactoperoxidase; NE: norepinephrine; RP-HPLC: reversed phase-high performance liquid chromatographic; SOD: superoxide dismutase; TCM: traditional Chinese medicine; UV: ultra-violet; VEGF: vascular endothelial growth factor; WGLE: wild ginseng leaf extract.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HWW, DCP and JTX conceived the topic, collected data and drafted the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

We thank R Flagg and DJ Spjergel for their comments on the manuscript.

References

- Chevallier A: **Encyclopedia of herbal medicine**. New York: DK Publishing Inc; 2000.
- Xie J-T, Attele AS, Yuan C-S: **Ginseng: beneficial and potential adverse effect**. In *A textbook of complementary and alternative therapies* Edited by: Yuan C-S, Deiber E, Bauer BA. Boca Raton, London, New York, Washington, DC: CRC Press Company; 2006:71-89.
- Sun XB, Matsumoto T, Yamada H: **Purification of an anti-ulcer polysaccharide from the leaves of Panax ginseng**. *Planta Med* 1992, **58**:445-448.
- Gillis CN: **Panax ginseng pharmacology: a nitric oxide link?** *Biochem Pharmacol* 1997, **54**(1):1-8.
- Li J, Huang M, Teoh H, Man RY: **Panax quinquefolium saponins protects low density lipoproteins from oxidation**. *Life Sci* 1999, **64**(1):53-62.
- Keum YS, Park KK, Lee JM, Chun KS, Park JH, Lee SK, Kwon H, Surh YJ: **Antioxidant and anti-tumor promoting activities of the methanol extract of heat-processed ginseng**. *Cancer Letters* 2000, **150**:41-48.
- Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA: **Recent patterns of medication use in the ambulatory adult population of the United States**. *JAMA* 2002, **287**:337-344.
- Kim YK, Guo Q, Packer L: **Free radical scavenging activity of red ginseng aqueous extracts**. *Toxicology* 2002, **172**:149-156.
- Seely D, Dugoua JJ, Perri D, Mills E, Koren G: **Safety and efficacy of panax ginseng during pregnancy and lactation**. *Can J Clin Pharmacol* 2008, **15**(1):87-94.
- Cheng TO: **Panax (ginseng) is not a panacea**. *Arch Intern Med* 2000, **160**:3329-3330.
- Attele AS, Wu JA, Yuan CS: **Ginseng pharmacology: multiple constituents and multiple actions**. *Biochem Pharmacol* 1999, **58**(11):1685-1693.
- Lim J-Y, Ishiguro K, Kubo I: **Tyrosinase inhibitory p-coumaric acid from ginseng leaves**. *Phytother Res* 1999, **13**:371-375.
- Li TSC, Mazza G, Cottrell AC, Gao L: **Ginsenosides in roots and leaves of American ginseng**. *J Agric Food Chem* 1996, **44**:717-720.
- Hou JP: **The chemical constituents of ginseng plants**. *Comp Med East and West* 1977, **5**:123-145.
- Yip TT, Lau CN, But PP, Kong YC: **Quantitative analysis of ginsenosides in fresh Panax ginseng**. *Am J Chin Med* 1985, **13**:77-88.
- Zhonghua Bencao Editors: **Zhonghua Bencao (Chinese Herbal Medicine)**. Shanghai: Shanghai Science and Technology House; 1996.
- Huang KC: **The Pharmacology of Chinese Herbs**. Boca Raton, FL: CRC Press; 1999.
- Yang XW, Li LY, Tian JM, Zhang ZW, Ye JM, Gu WF: **Ginsenoside-Rg₆, a novel triterpenoid saponin from the stem-leaves of Panax ginseng C. A. Mey.** *Chinese Chemical Letters* 2000, **11**:909-912.
- Dou DQC, Liang YJ, Pang LH, Shimizu FG, N Takeda T: **Six new dammarane-type triterpene saponins from the leaves of Panax ginseng**. *Chem Pharm Bull* 2001, **49**:442-446.
- Ma XQ, Liang XM, Xu Q, Zhang XZ, Xiao HB: **Identification of ginsenosides in roots of Panax ginseng by HPLC-APCI/MS**. *Phytochem Anal* 2005, **16**(3):181-187.
- Xie JT, Mehendale SR, Wang A, Aung HH, Wu J, Osinski J, Yuan C-S: **American ginseng leaf: Ginsenoside analysis and hypoglycemic activity**. *Pharmacol Res* 2004, **49**:113-117.
- Li TSCWD: **Seasonal fluctuations of leaf and root weight and ginsenosides contents of 2-, 3-, and 4-year-old American ginseng plants**. *HortTechnology* 2002, **12**:229-232.
- Jackson CJC, Dini JP, Lavandier C, Faulkner H, Rupasinghe HPV, Proctor JTA: **Ginsenoside content of North American ginseng (Panax quinquefolius L. Araliaceae) in relation to plant development and growing locations**. *J Ginseng Research* 2003, **27**:135-140.
- Assinewe VA, Baum BR, Gagnon D, Arnason JT: **Phytochemistry of Wild Populations of Panax quinquefolius L. (North American Ginseng)**. *J Agric Food Chem* 2003, **51**:4549-4553.
- Wang CZ, Wu JA, McEntee E, Yuan CS: **Saponin composition in american ginseng leaf and berry assayed by high-performance liquid chromatography**. *J Agric Food Chem* 2006, **54**(6):2261-2266.
- Li XW, Gui MY, Zheng Y, Jin YR, Zhang HQ: **[Determination of 20 (S)-ginsenoside Rh2 in the alkali-hydrolysis product of saponins from leaves of Panax quinquefolium by RP-HPLC]**. *Zhongguo Zhong Yao Za Zhi* 2006, **31**(5):386-388.
- Shi W, Wang Y, Li J, Zhang H, Ding L: **Investigation of ginsenosides in different parts and ages of Panax ginseng**. *Food Chemistry* 2007, **102**:664-668.
- Yan B, Wang G, A J, Xie L, Hao H, Liang Y, Sun J, Li X, Zheng Y: **Construction of the fingerprints of ginseng stem and leaf saponin reference substances and spiked plasma sample by LC-ESI/MS and its application to analyzing the compounds absorbed into blood after oral administration of ginseng stem and leaf saponin in rat**. *Biol Pharm Bull* 2007, **30**(9):1657-1662.
- Wu LJ, Wang LB, Gao HY, Wu B, Song XM, Tang ZS: **A new compound from the leaves of Panax ginseng**. *Fitoterapia* 2007, **78**(7-8):556-560.
- Saqito H, Morita M, Takagi K: **Pharmacological studies of panax ginseng leaves**. *Japan J Pharmacol* 1973, **23**:43-56.
- Wang BX, Cui JC, Liu AJ: **Antidiuretic effect of ginsenosides of the stems and leaves of Panax ginseng (author's transl)**. *Zhongguo Yao Li Xue Bao* 1980, **1**(2):126-130.
- Wang BX, Cui JC, Liu AJ: **The action of ginsenosides extracted from the stems and leaves of Panax ginseng in promoting animal growth**. *Yao Hsueh Hsueh Pao* 1982, **17**(12):899-904.
- Wang A, Gao Y, Wang Y, Zhao R, Liu C: **Effects of Chinese ginseng root and stem-leaf saponins on learning, memory and biogenic monoamines of brain in rats**. *Zhongguo Zhong Yao Za Zhi* 1995, **20**:493-495.
- Ma TC, Yu QH, Chen MH: **Effects of ginseng stem-leaf saponins on one-way avoidance behavior in rats**. *Acta Pharmacol Sinica* 1991, **12**:403-406.
- Deyama TN, S Najazawa Y: **Constituents and pharmacological effects of Eucommia and Siberian ginseng**. *Acta Pharmacol Sin* 2001, **22**:1057-1070.

36. Song C-SR, Shi Y, Song J, Tian J-J, Guo J-Z, J Dai X, Yang J-D: **Effect of qutan huoluo jiannaoyao preparation in improving memory impairment of rats with cerebral ischemia.** *Chinese Journal of Clinical Rehabilitation* 2006, **10**:32-35.
37. Li M, Ling CQ, Huang XQ, Shen ZL: **Effects of ginsenosides extracted from ginseng stem and leaves on glucocorticoid receptor in different viscera in heat-damaged rats.** *Zhong Xi Yi Jie He Xue Bao* 2006, **4**(2):156-159.
38. Petkov VD, Cao Y, Todorov I, Lazarova M, Getova D, Stancheva S, Alova L: **Behavioral effects of stem-leaves extract from *Panax ginseng* C. A. Meyer.** *Acta Physiol Pharmacol (Bulg)* 1992, **18**:41-48.
39. Sui DY, Yu XF, Qu SC, Lu ZZ, Wang L, Chen MQ: **Protective effect of *Panax quinquefolium* 20s-proto-panaxdiolsaponins on acute myocardial infarction in dogs.** *Zhongguo Zhong Yao Za Zhi* 2001, **26**(6):416-419.
40. Wang CL, Shi DZ, Yin HJ: **Effect of panax quinquefolium saponin on angiogenesis and expressions of VEGF and bFGF in myocardium of rats with acute myocardial infarction.** *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2007, **27**(4):331-334.
41. Zhang J-M, Matsuura Y, Sueda T, Orihashi K: **Beneficial effects of ginsenosides of stems and leaves on cardiac and coronary vascular functions after 12-hour rat heart preservation.** *Transplantation proceedings* 1999, **31**:2175-2178.
42. Guan L, Yi X, Feng Q, Yang L: **Effects of saponins from stems and leaves of *Panax quinquefolium* L. on the contraction of rabbit aortic strips.** *Zhongguo Zhong Yao Za Zhi* 1996, **20**:431-434.
43. Chen X, Yang SJ, Chen L, Ma XL, Chen YP, Wang LL, Sun CW: **The effects of *Panax quinquefolium* saponin (PQS) and its monomer ginsenoside on heart.** *Zhongguo Zhong Yao Za Zhi* 1994, **19**(10):617-620.
44. Hu JX, Jia GX, Yan ZR: **Clinical and experimental study of shen-shao tongguan pian in treating angina pectoris of coronary heart disease.** *Zhong Xi Yi Jie He Za Zhi* 1990, **10**:596-599.
45. Hong M: **Effects of ageing and ginsenoside on atrial natriuretic peptide gene expression.** *Zhonghua Yi Xue Za Zhi* 1991, **71**:140-143.
46. Hong M, Jin Y, Mai YQ, Boersma A, Han KK, Vantighem MC, Lefebvre J: **The decline of atrial natriuretic peptide (ANP) gene expression in older rats and the effects of ginsenoside on ANP gene expression.** *Comp Biochem Physiol B* 1992, **101**:35-39.
47. Yang Y, Wu T, He K, Fu ZG: **Effect of aerobic exercise and ginsenosides on lipid metabolism in diet-induced hyperlipidemia mice.** *Acta Pharmacol Sin* 1999, **20**:563-565.
48. Wen Y, Pei Y, Chen Y, Wang Z, Ma Z, Wang M, Li W: **Effects of ginsenosides from stems and leaves on hyperlipemia induced by prednisone acetate in rabbits.** *Zhongguo Zhong Yao Za Zhi* 1996, **21**:430-431.
49. Shane-McWhorter L, Oderda LH: **Importance of cultural issues in managing a patient with diabetes.** *Consult Pharm* 2007, **22**(5):431-437.
50. Sotaniemi EA, Haapakoski E, Rautio A: **Ginseng therapy in non-insulin-dependent diabetic patients.** *Diabetes Care* 1995, **18**(10):1373-1375.
51. Vuksan V, Sievenpiper JL, Koo VY, Francis T, Beljan-Zdravkovic U, Xu Z, Vidgen E: **American ginseng (*Panax quinquefolium* L) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes mellitus.** *Arch Intern Med* 2000, **160**(7):1009-1013.
52. Vuksan V, Sievenpiper JL, Xu Z, Wong EY, Jenkins AL, Beljan-Zdravkovic U, Leiter LA, Josse RG, Stavro MP: **Konjac-Mannan and American ginseng: emerging alternative therapies for type 2 diabetes mellitus.** *J Am Coll Nutr* 2001, **20**(5 Suppl):370S-380S. discussion 381S-383S
53. Chung SH, Choi CG, Park SH: **Comparisons between white ginseng radix and rootlet for antiatherogenic activity and mechanism in KKAY mice.** *Arch Pharm Res* 2001, **24**(3):214-218.
54. Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, Pugh W, Rue PA, Polonsky KS, Yuan CS: **Antidiabetic effects of *Panax ginseng* berry extract and the identification of an effective component.** *Diabetes* 2002, **51**(6):1851-1858.
55. Xie JT, Aung HH, Wu JA, Attele AS, Yuan CS: **Effects of American ginseng berry extract on blood glucose levels in ob/ob mice.** *Am J Chin Med* 2002, **30**(2-3):187-194.
56. Xie JT, Zhou Y-P, Dey L, Attele A, Wu J, Gu M, Polonnsky K, Yuan C: **Ginseng berry reduces blood glucose and body weight in db/db mice.** *Phytomedicine* 2002, **9**:254-258.
57. Molokovskii DS, Davydov VV, Tiulenev VV: **The action of adaptogenic plant preparations in experimental alloxan diabetes.** *Probl Endokrinol (Mosk)* 1989, **35**(6):82-87.
58. Broadhurst CL, Polansky MM, Anderson RA: **Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro.** *J Agric Food Chem* 2000, **48**(3):849-852.
59. Davydov VV, Molokovskii DS, Limarenko A: **Efficacy of ginseng drugs in experimental insulin-dependent diabetes and toxic hepatitis.** *Patol Fiziol Eksp Ter* 1990:49-52.
60. Xie JT, Wang CZ, Wang AB, Wu J, Basila D, Yuan CS: **Antihyperglycemic effects of total ginsenosides from leaves and stem of *Panax ginseng*.** *Acta Pharmacol Sin* 2005, **26**(9):1104-1110.
61. Xie JTWC, Ni M, Wu JA, Mehendale SR, Aung HH, Yuan CS: **American ginseng berry juice intake reduces blood glucose and body weight in ob/ob mice.** *J Food Sci* 2007, **72**(8):S590-S594.
62. Park HSKT, Moon DG, Kim JJ, Cheon J: **Development of the novel anti-cancer immunotherapy for human prostate cancer: In vivo characterization of an immunotropic and anti-cancer activities of the new polysaccharide from the leaves of *Panax ginseng* C.A. Meyer.** *Eur Urol Suppl* 3 2004:365-366.
63. Widodo N, Takagi Y, Shrestha BG, Ishii T, Kaul SC, Wadhwa R: **Selective killing of cancer cells by leaf extract of *Ashwagandha*: Components, activity and pathway analyses.** *Cancer Lett* 2008, **262**:37-47.
64. Zhang QH, Wu CF, Duan L, Yang JY: **Protective effects of total saponins from stem and leaf of *Panax ginseng* against cyclophosphamide-induced genotoxicity and apoptosis in mouse bone marrow cells and peripheral lymphocyte cells.** *Food Chem Toxicol* 2008, **46**(1):293-302.
65. Kitts DD, Popovich DG, Hu C: **Characterizing the mechanism for ginsenoside-induced cytotoxicity in cultured leukemia (THP-1) cells.** *Can J Physiol Pharmacol* 2007, **85**(11):1173-1183.
66. Kitts DD, Wijewickreme AN, Hu C: **Antioxidant properties of a North American ginseng extract.** *Mol Cell Biochem* 2000, **203**:1-10.
67. Dou DQ, Chen YJ, Liang LH, Pang FG, Shimizu N, Takeda T: **Six new dammarane-type triterpene saponins from the leaves of *Panax ginseng*.** *Chem Pharm Bull (Tokyo)* 2001, **49**(4):442-446.
68. Jung CH, Seog HM, Choi IW, Choi HD, Cho HY: **Effects of wild ginseng (*Panax ginseng* C.A. Meyer) leaves on lipid peroxidation levels and antioxidant enzyme activities in streptozotocin diabetic rats.** *J Ethnopharmacol* 2005, **98**(3):245-250.
69. Jung C-HS, H-M Choi I-W, Cho H-Y: **Antioxidant activities of cultivated and wild Korean ginseng leaves.** *Food Chemistry* 2005, **92**:535-540.
70. Jung C-HS, H-M Choi I-W, Park M-W, Cho H-Y: **Antioxidant properties of various solvent extracts from wild ginseng leaves.** *LWT* 2006, **39**:266-274.
71. Jiang Y, Zhong GG, Chen L, Ma XY: **Influences of ginsenosides Rb1, Rb2, and Rb3 on electric and contractile activities of normal and damaged cultured myocardocytes.** *Zhongguo Yao Li Xue Bao* 1992, **13**(5):403-406.
72. Wang B, Cui J, Liu A, Wu S: **Studies on the anti-fatigue effect of the saponins of stems and leaves of panax ginseng (SSLG).** *J Tradit Chin Med* 1983, **3**:89-94.
73. Wang B, Cui J, Liu A: **Antidiuretic effect of ginsenosides of the stems and leaves of *Panax ginseng*.** *Acta Pharmacol Sin* 1980, **1**:126-130.
74. Zhou L, Hao R, Jjiang L: **Clinical study on retarding aging effect of tongbu recipe to traditional Chinese medicine.** *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1999, **19**:218-220.
75. Yi RL, Li W, Hao XZ: **Inductive differentiation effect of ginsenosides on human acute nonlymphocytic leukemia cells in 58 patients.** *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1993, **13**:722-724.
76. Singh B, Saxena AK, Chandan BK, Gupta DK, Bhutani KK, Anand KK: **Adaptogenic activity of a novel, withanolide-free aqueous fraction from the roots of *Withania somnifera* Dun.** *Phytother Res* 2001, **15**:311-318.
77. Klepser TB, Klepser ME: **Unsafe and potentially safe herbal therapies.** *Am J Health Sys Pharm* 1999, **56**:125-138.
78. Xie JT, Mehendale S, Malecar S: **Is ginseng free from adverse effects?** In *A Textbook of Complementary and Alternative Therapies* Edited by: Yuan C-S, Beiber E. Boca Raton: CRC Press Company; 2002:219-224.

79. Coon JT, Ernst E: **Panax ginseng : a systematic review of adverse effects and drug interactions.** *Drug Saf* 2002, **25**:323-344.
80. Siegel RK: **Ginseng abuse syndrome. Problems with the panacea.** *JAMA* 1979, **241**(15):1614-1615.
81. Nocerino E, Amato M, Izzo A: **The aphrodisiac and adaptogenic properties of ginseng.** *Fitoterapia* 2002, **71**:S1-S5.
82. Morgan A, Cupp MJ: **Panax ginseng.** In *Toxicology and clinical pharmacology of herbal products* Edited by: Cupp MJ. Totowa, NJ: Humana Press; 2002:141-153.
83. Ang-Lee MKM, J Yuan C-S: **Herbal Medicines and perioperative care.** *JAMA* 2001, **286**:208-216.
84. Saito H, Morita M, Takagi K: **Pharmacological studies of Panax Ginseng leaves.** *Jpn J Pharmacol* 1973, **23**(1):43-56.

Publish with **BioMed Central** and every scientist can read your work free of charge

"BioMed Central will be the most significant development for disseminating the results of biomedical research in our lifetime."

Sir Paul Nurse, Cancer Research UK

Your research papers will be:

- available free of charge to the entire biomedical community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
http://www.biomedcentral.com/info/publishing_adv.asp

