

GINSENG PHARMACOLOGY: MULTIPLE MOLECULAR TARGETS AND RECENT CLINICAL TRIALS

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SUMMARY

Ginseng has been used as a folk medicine in Far East Asian countries for several thousand years. Recently, its use has also expanded to Western countries. A number of studies provide evidence for its various pharmacological properties, including antifertility, antidiabetic, antiobesity, antibacterial, antifungal, antiviral, antiulcer and neuroprotective effects. Ginseng and its constituents have demonstrated the ability to interact with multiple molecular targets affecting multistep processes in many diseases. Research revealed that ginseng and its constituents bind to a variety of proteins and inhibit the activity of various kinases. Ginseng also modulates the activity of various transcription factors, enzymes, receptors, ion channels, antiapoptotic proteins, adhesion molecules and others, including different cyclins. Various beneficial in vitro and in vivo effects in different pathological conditions have encouraged researchers to design clinical trials to investigate the safety, efficacy and pharmacokinetics of ginseng. The clinical trials have provided encouraging results, and a number of other trials are in progress. This study aims to review the various beneficial effects of ginseng in different pathological conditions. The multiple molecular targets for ginseng published in the literature during the past few years are included. Similarly, the completed or ongoing clinical trials for ginseng and its constituents are also summarized.

INTRODUCTION

Ginseng, a member of the Araliaceae family, is a slow-growing perennial herb with fleshy roots. Eleven major species of this plant have been reported in the literature (1). However, the majority of studies are concerned with the constituents from three common species, *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng) and *Panax japonicus* (Japanese ginseng) (2). Ginseng root has been used as a folk medicine in Far East Asian countries for several thousand years, with the belief that it cures all diseases (3). During the last few decades, its use has extended to Western countries for the improvement of various conditions.

The bioactive constituents isolated from various ginseng species include ginsenosides, polysaccharides, peptides, nucleic acids, alkanes, alkynes, sterols, monoterpenes, sesquiterpenes, phenylpropanoids, chromones, amines, flavonoids, organic acids, vitamins, enzymes, inorganic compounds, polyacetylenic alcohols and fatty acids (1, 3). Among these, ginsenosides are considered to be the main constituents responsible for various molecular actions of ginseng. There is a wide variation in the relative abundance of ginsenoside content in various ginseng species. To date, more than 100 bioactive compounds have been reported from different ginseng species (4).

Research has revealed that ginseng has a wide array of pharmacological properties, including antioxidant, anticancer, anti-inflammatory, antiapoptotic, antihepatotoxic, antimutagenic, antifertility, antidiabetic, antibacterial, antifungal, antiviral, antiulcer and neuroprotective effects. During the last decade, there has been additional interest in studying the molecular pharmacology of ginseng and its constituents using various modern biological methods, including molecular, biochemical and electrophysiological techniques. These studies have demonstrated that ginseng has multiple actions through direct and indirect interaction with various molecular players (5). Numerous molecular targets for ginseng have been identified using these techniques. Recently, it has been demonstrated by our group that ginseng extracts improved visual sensitivity and may have beneficial effects in ophthalmic diseases (6). As ginseng has shown promising results in in vitro and in vivo preclinical studies,

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several trials were initiated to address the safety, efficacy and pharmacokinetics of ginseng at the clinical level.

The purpose of this article is to review the beneficial in vitro and in vivo effects of ginseng in different pathological conditions. Numerous molecular targets for ginseng identified through extensive molecular research are summarized. The clinical studies conducted over the past few years are also highlighted.

BIOLOGICAL AND PHARMACOLOGICAL EFFECTS OF GINSENG

In folk medicine, ginseng and its constituents have been used as therapeutic preparations over the past few thousand years in different parts of the world. In the traditional Chinese medical book, *Shen Nong Ben Cao Jing*, ginseng has well-documented pharmacological properties, such as curative, stimulant and antiaging effects, as well as a long list of other activities. A full discussion of the traditional medicinal uses of ginseng is beyond the scope of this review.

Recent investigation suggests that ginseng has modulatory effects in various diseases (Fig. 1). Since the anticancer, antiapoptotic, antimutagenic, neuroprotective and central nervous system (CNS) effects of ginseng have been well documented in other review articles, these will not be discussed here.

Effects on gastrointestinal and cardiovascular systems

P. ginseng has been reported to exhibit gastroprotective activity in peptic and chronic ulcer models (7). Later, it was found that ginsenoside Rb1 is the main constituent responsible for the antiulcer activity of ginseng through an increase in mucus secretion (8). Ginseng and ginsenosides improve the accelerated movement of the small intestine and contribute to the action of Dai-kenchu-to on small intestinal transit (9). Additionally, ginseng has shown antihepatotoxic effects in vitro and in vivo (10).

The beneficial effects of ginseng in cardiovascular diseases are well documented. Ginseng and its main active constituents exhibit a variety of cardiovascular actions, including antihypertensive, negative chronotropic, negative inotropic, vasorelaxant and antiarrhythmic effects, and protection against ischemia/reperfusion injury. Moreover, ginsenosides protect against myocardial infarction (11, 12).

Antibacterial, antifungal and antiviral effects of ginseng

A pilot study on standardized G115 ginseng extract revealed its beneficial effects on the reduction in bacterial counts in the bronchial system of patients with acute attacks of chronic bronchitis (13). In another study, ginseng treatment reduced bacterial load in chronic *Pseudomonas aeruginosa* pneumonia in rats (14).

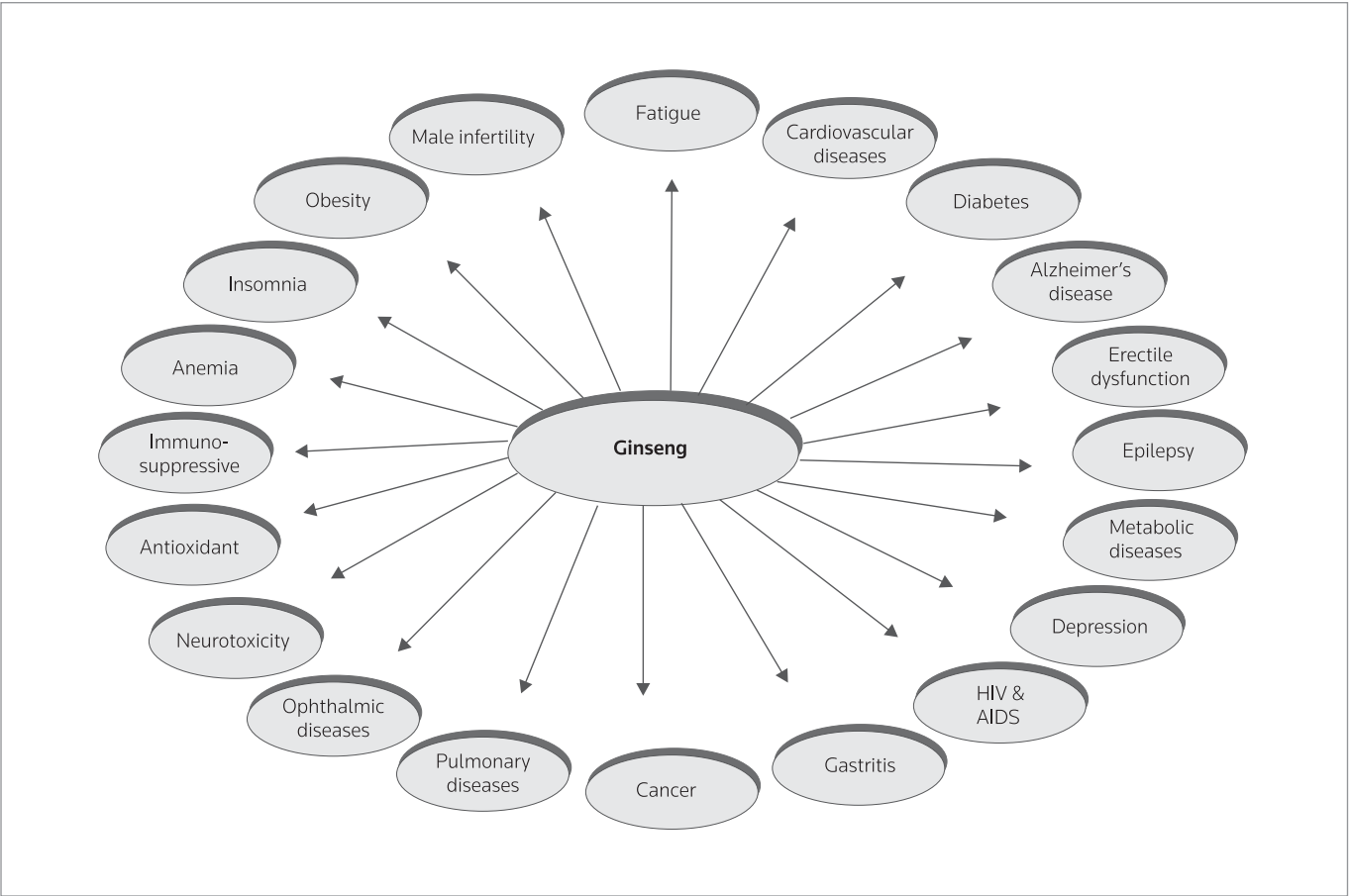


Figure 1. Various diseases in which ginseng has beneficial effects (for references see text).

The antifungal activity of ginseng has recently been investigated. *Panax notoginseng* RNase exhibits antifungal activity against *Phylospora piricola* and *Coprinus comatus* (15). Recent investigations suggest that ginsenosides exert considerable antifungal activity by disrupting the structure of the cell membrane (16).

Ginseng and its constituents have also been shown to have antiviral activity. In an early study, *P. ginseng* extract was found to be effective against experimental Semliki Forest virus infection in mice (17). In a more recent report, it was observed that panaxagin, a protein from Chinese ginseng, exhibits antiviral activity (18); panaxagin exerted its activity through inhibition of the HIV reverse transcriptase enzyme. In 2004, a study reported that ginsenoside Rb1 from *P. ginseng* demonstrated antiviral activity at a concentration of 100 μ M (19). Most importantly, clinical studies have revealed that Korean red ginseng delays disease progression in HIV-1-infected patients (20).

Antifertility, antidiabetic and antiobesity effects of ginseng

There is evidence that ginseng has a potent effect on fertility functions (21, 22), as well as beneficial effects on erectile dysfunction and premature ejaculation (22, 23). *P. ginseng* extract showed an improvement in spermatozoa number/mL and progressive oscillating motility, an increase in plasma total and free testosterone, dihydrotestosterone, follicle-stimulating hormone and luteinizing hormone levels (24). Another study revealed that diabetic rats with decreased erectile function showed better erectile responses to cavernosal nerve stimulation upon treatment with Korean red ginseng (23).

Ginseng has been widely studied for the treatment of diabetes and obesity in animal models and human patients. Ginseng and its constituents have beneficial effects in the regulation of blood glucose and blood pressure. Intriguingly, in addition to ginseng root, ginseng berry and leaf were also shown to reduce blood glucose and body weight in models of diabetes and obesity (25). In diabetic (*ob/ob*) mice the berry ginseng extract produced a significant reduction in hyperglycemia and fasting and postprandial insulin levels, while glucose tolerance was markedly improved. It was also found that ginseng berry extract reduced food intake, decreased body weight and enhanced energy expenditure, as indicated by increased body temperature (26). The efficacy of berry extract was also examined in *db/db* mice, and good results were observed on glucose and energy metabolism. The extract also reduced body weight in lean littermates, indicating that ginseng has beneficial effects in both lean and genetically obese mice (27).

Another study compared the effects of ginseng root and ginseng berry on metabolic syndrome in *ob/ob* mice (28). The results suggested that ginseng berry has more potent effects than ginseng root in decreasing blood glucose, increasing glucose tolerance and lowering body weight. Ginseng leaf also has antidiabetic and antiobesity effects, as demonstrated in *ob/ob* mice (29). It was found that the leaf extracts lower blood glucose levels, raise body temperature and reduce body weight after injections over 12 days.

Anti-inflammatory activity of ginseng

Several investigators used ginseng or its active constituents to treat inflammation in animals and humans. Published results revealed

that ginseng could effectively inhibit inflammation. The anti-inflammatory role of ginseng might be due to the effects of ginsenosides, as they target different levels of immunological activity, and so contribute to the diverse actions of ginseng in humans (30). A recent study concluded that ginseng has potential analgesic and anti-inflammatory activities. The results confirmed the pharmacological effects of ginseng for the relief of pain and inflammation. This study also suggested that the anti-inflammatory activity of ginseng may be due to inhibition of cyclooxygenases and/or lipoxygenases (31).

MULTIPLE MOLECULAR TARGETS OF GINSENG

Ginseng has a diverse range of molecular targets, which include transcription factors, growth factors and their receptors, genes regulating cell proliferation and apoptosis, cytokines, enzymes, ion channels and neuronal receptors (Table I).

It can be concluded from published results that ginseng and its constituents are effective inhibitors of the activation of various transcription factors, including nuclear factor NF- κ B, transcription factor AP-1, signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor PPAR γ and β -catenin (32-34). The aforementioned transcription factors regulate the expression of genes that play an important role in tumorigenesis, cell survival, invasion, cell proliferation, inflammation and angiogenesis.

The misregulation of a variety of tyrosine and other kinases has been found to contribute to the development of various disease conditions. Experimentally, it was shown that ginseng and its constituents regulate the activity of various tyrosine-protein kinases. Ginseng treatment attenuated the expression of epidermal growth factor receptor (EGFR, erbB-1), erbB-2 (HER2) and apoptosis regulator Bcl-2, as well as the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, serine/threonine-protein kinase Akt and extracellular signal-regulated kinase (ERK) signaling pathways (32-35). Ginseng also modulated the activity of other kinases, including phosphorylase kinase, protein kinase C (PKC), protamine kinase, autophosphorylation-activated protein kinase and tyrosine-protein kinase Src (36-38). It was reported that ginseng can completely inhibit the activity of various protein kinases, including EGFR, ERK, PKA, PKB, PKC and Janus kinase (30, 39). On the other hand, it activates the c-Jun N-terminal kinase and mitogen-activated protein kinase (MAPK) (32).

Ginseng can interact and alter the activities of various growth factors. Ginseng and its constituents especially target EGF, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor- β (TGF- β) and many others that are linked with growth signaling and cell proliferations (34, 40). Ginseng can induce apoptosis through decreased expression of proapoptotic proteins, particularly vascular endothelial growth factor (VEGF) (41).

It has been reported that ginsenosides increase DNA polymerase activity 2.2-fold in a concentration-dependent manner (42). Other studies have provided evidence that ginseng and its constituents have the ability to interact with other enzymes, including cyclooxygenase-2 (COX-2), lipoxygenase (LOX), nitric oxide synthase (NOS), heme oxygenase 1 (HO-1), and others that are necessary for the normal activity of cells and tissues (5, 30, 31, 34, 43).

Table I. A list of multiple molecular targets of ginseng.

| Molecular targets | Reference |
|--|-----------|
| <i>Transcriptional factors</i> | |
| Transcription factor AP-1 | 32, 36 |
| β -Catenin | 33 |
| CREB-binding protein | 65 |
| Hypoxia inducible factor 1 | 41 |
| Nuclear factor NF- κ B | 34 |
| Peroxisome proliferator-activated receptor PPAR γ | 34, 66 |
| Signal transducer and activator of transcription STAT-1, -3, -4 and -5 | 40, 67 |
| <i>Kinases</i> | |
| Autophosphorylation-activated protein kinase | 36 |
| c-Jun N-terminal kinase | 30 |
| Epidermal growth factor receptor | 39 |
| Extracellular signal-regulated kinase | 39 |
| Focal adhesion kinase | 68 |
| IL-1 receptor-associated kinase | 30 |
| Janus kinase | 30 |
| Mitogen-activated protein kinase | 68 |
| Phosphorylase kinase | 36 |
| Protamine kinase | 37 |
| Protein kinase A, B and C | 30 |
| Tyrosine-protein kinase Src | 38 |
| <i>Growth factors</i> | |
| Connective tissue growth factor | 69 |
| Fibroblast growth factor | 70 |
| Hepatocyte growth factor | 71 |
| Nerve growth factor | 72 |
| Platelet-derived growth factor | 69 |
| Transforming growth factor- β | 34, 70 |
| Vascular endothelial growth factor | 41 |
| <i>Enzymes</i> | |
| ATPase | 5 |
| Cyclooxygenases | 34 |
| DNA polymerase | 5 |
| Glutathione S-transferase | 73 |
| Glutamate-cysteine ligase | 74 |
| Glutamyl cysteine ligase | 75 |
| Heme oxygenase-1 | 30 |
| Inducible nitric oxide synthase | 43 |
| Lipoxygenase | 31 |
| Matrix metalloproteinase | 30 |
| Ornithine decarboxylase | 76 |
| Telomerase | 77 |
| <i>Cytokines</i> | |
| Interleukins | 41 |
| Monocyte chemoattractant protein | 30 |
| Migration inhibitory protein | 71 |
| Tumor necrosis factor TNF- α | 34 |
| <i>Receptors</i> | |
| Androgen receptor | 70 |
| Aryl hydrocarbon receptor | 78 |
| Death receptor 5 | 79 |
| Epidermal growth factor receptor | 80, 81 |
| Estrogen receptor | 70 |
| Fas receptor | 79 |
| Glucocorticoid receptor | 70 |
| Histamine H ₂ receptor | 81 |
| Inositol 1,4,5-triphosphate receptor | 82 |
| Integrin receptor | 70 |
| Progesterone receptor | 70 |
| Urokinase plasminogen activator surface receptor | 70 |

Continued

Table I. Cont. A list of multiple molecular targets of ginseng.

| Molecular targets | Reference |
|--|-----------|
| <i>Adhesion molecules</i> | |
| Endothelial leukocyte adhesion molecules | 70 |
| Intercellular adhesion molecule 1 | 70 |
| Vascular cell adhesion protein 1 | 70 |
| <i>Proteins</i> | |
| Apoptosis regulator Bcl-2 | 35 |
| Bcl-X(L) | 35 |
| High-density lipoprotein | 70 |
| Low-density lipoprotein | 70 |
| Uncoupling protein 2 | 45 |
| <i>Ion channels</i> | |
| GABA receptor channels | 47 |
| Glucocorticoid receptor channels | 5 |
| Glycine receptor α 1 receptor channels | 48 |
| Human 5-HT _{3A} receptor channels | 48 |
| Nicotinic acetylcholine receptor channels | 46 |
| NMDA receptor channels | 48 |
| Sodium, potassium and calcium voltage-gated channels | 46 |
| <i>Other</i> | |
| Cyclin D1, E and cyclin-CDK complex | 35, 36 |
| Glutamate-induced neurodegeneration | 48 |
| Heat shock proteins | 83 |
| Kainate-induced cell damage | 48 |
| Multidrug resistance protein | 70 |
| p53 and p21 | 34, 36 |
| Retinal neuronal antagonist | 6 |
| Urokinase-type plasminogen activator | 70 |

In addition, ginseng effectively regulates the activity of various hormones. An investigation suggested that ginseng inhibits cytokine-induced apoptosis in β -cells (44). In a mouse model, ginseng modulated Th1-like immune responses in mice with *Pseudomonas aeruginosa* lung infection (45). Furthermore, higher levels of interferon gamma (IFN- γ) and TNF- α and lower levels of interleukin-4 (IL-4) cytokines were observed after ginseng treatment. Other studies reported that ginseng can effectively interact with and modulate the activity of various inflammatory cytokines, including interleukins IL-1, -2, -5, -6, -8, -12 and -18 (41).

Recent electrophysiological studies suggested that ginseng and its constituents bind and regulate the activity of a variety of ion channels and receptors. It was reported that ginseng can attenuate the sodium, potassium and calcium voltage-gated ion channels (46). It can alter ligand-gated ion channels such as nicotinic acetylcholine, glucocorticoid, GABA, glycine receptor α 1 and 5-HT_{3A} receptors and NMDA receptor channel activity (46-48). Additionally, a recent study by our group has shown that ginseng possesses retinal neuronal antagonist activity (6).

It can be concluded that the diverse in vitro and in vivo pharmacological activities of ginseng might be due to its ability to mediate multiple molecular targets. Additionally, the multiple molecular targets and multifaceted pharmacological functions of ginseng combined can explain its role in different diseases. Thus, these properties made ginseng a desirable choice for clinical use in the treatment of various diseases.

GINSENG IN HUMAN CLINICAL TRIALS

In response to the increasing in vitro and in vivo evidence for the beneficial effects of ginseng and its constituents, a number of clinical studies have been carried out to address its safety, efficacy and pharmacokinetics. Promising results have been reported in patients treated with ginseng extract, isolated fractions or pure constituents. These trials assessed the effects of ginseng on physical and psychomotor performance, cognitive function, type 2 diabetes, obesity, upper respiratory infection, allergic conditions, various types of cancer and immunomodulation. Diseases in which the beneficial effects of ginseng have been evaluated in the past few years are summarized in Table II. Early trials were focused on the efficacy of ginseng, while the current studies are also exploring the safety and pharmacokinetics (49).

Clinical studies on the effects of ginseng on physical and psychomotor performance and cognitive function showed controversial results. Therefore, further pilot and well-controlled studies are needed to fully evaluate the efficacy of ginseng in the above-mentioned dis-

eases (33, 50). Clinical results for immunomodulation were encouraging. Results from a study in 60 volunteers showed enhancement of chemotaxis, phagocytosis, total lymphocyte count and numbers of T helper cells after 8 weeks of treatment with G115 extract at a dose of 100 mg twice daily (51). In a pilot study, 36 patients with newly diagnosed non-insulin-dependent diabetes were subjected to 8 weeks of ginseng treatment at a dose of 100 or 200 mg. Results showed improvement in psychophysical performance and reduction in fasting blood glucose and body weight. Additionally, elevated mood and other favorable symptoms were also observed after ginseng treatment (52).

Ginseng also displayed promising results in other clinical studies, such as increasing the energy level in cancer patients and other patients. Although most of the results published in the literature regarding the efficacy of ginseng are encouraging, there are also studies which did not achieve the goal for ginseng therapy. Despite intense research efforts, only little is known about the safety and pharmacokinetics of ginseng. However, it may be a prime time for

Table II. A list of completed and ongoing clinical trials of ginseng.

| Disease | Study type/design | No. of patients | Start date and present condition | Trial site | ClinicalTrials.gov Identifier* |
|---|-----------------------------|-----------------|---|---|--------------------------------|
| Alzheimer's disease, Memory decline | (Phase I&II), nonrandomized | ? | April 2004 completed October 2005 | Seoul National University Hospital, KR | NCT00391833 |
| Breast cancer | (Phase II), nonrandomized | 50 | February 2008 and ongoing | Simmons Cooper Cancer Institute, SIU School of Medicine, US | NCT00631852 |
| Cancer survivor, Infertility, Reproductive issues, Solid tumors | Randomized | 186 | May 2007 and ongoing | US-based locations National Cancer Institute | NCT00459134 |
| Diabetes type 2 | Phase II, randomized | 120 | September 2008 and ongoing | Clinical Nutrition and Risk Factor Modification Centre, Toronto, CA | NCT00728403 |
| Diabetes | (Phase 0), randomized | 19 | September 2003 completed September 2008 | Washington University School of Medicine, St. Louis, US | NCT00781534 |
| Fatigue, Solid tumors | Randomized | 280 | October 2005 | National Cancer Institute | NCT00182780 |
| Healthy volunteers | (Phase IV), randomized | 150 | January 2005 completed September 2009 | National Institutes of Health Clinical Center, Bethesda, US | NCT00103012 |
| Healthy volunteers | (Phase II), randomized | 60 | March 2020 completed March 2005 | University of Kansas Medical Center, Kansas City, US | NCT00029692 |
| Hypertension, Blood pressure, Endothelial function | Phase II, randomized | 17 | November 2007 | St. Michael's Hospital, Toronto, CA | NCT00728221 |
| Hypertension | (Phase III), randomized | 52 | April 2001 completed October 2003 | St. Michael's Hospital, Toronto, CA | NCT00219960 |
| Hypertension | (Phase II), randomized | 18 | June 2007 completed March 2008 | St. Michael's Hospital, Toronto, CA | NCT00730951 |
| Hyperglycemia | (Phase III), randomized | 12 | June 2005 completed July 2005 | St. Michael's Hospital, Toronto, CA | NCT00367926 |
| Ischemic stroke | (Phase II), randomized | 199 | September 2005 completed September 2006 | Xijing Hospital, Xi'an, CN | NCT00591084 |
| Ischemic stroke | (Phase III), randomized | 390 | September 2006 completed September 2008 | Xijing Hospital, Xi'an, CN | NCT00815763 |

Continued

Table II. Cont. A list of completed and ongoing clinical trials of ginseng.

| Disease | Study type/design | No. of patients | Start date and present condition | Trial site | ClinicalTrials.gov Identifier* |
|---|----------------------------|-----------------|--|---|--------------------------------|
| Leukemia | (Phase III), nonrandomized | 336 | September 2008 and ongoing | 130 worldwide locations National Cancer Institute | NCT00752895 |
| Multiple sclerosis | Phase II, randomized | 56 | September 2005 and ongoing | Oregon Health & Science University, Portland, US | NCT00754832 |
| Multiple cancer types, Fatigue | (Phase III), randomized | 360 | October 2008 and ongoing | 313 worldwide locations National Cancer Institute | NCT00719563 |
| Memory, Learning, Attention, Cognition, Well-being | (Phase II), randomized | 72 | Completed | Edmonton, CA | NCT00527969 |
| Postoperative ileus | (Phase II), randomized | 24 | December 2005 completed January 2008 | Washington University School of Medicine, St. Louis, US | NCT00266461 |
| Periodontitis | (Phase II), randomized | ? | Completed | The Oregon Health Sciences University, Portland, US | NCT00010634 |
| Schizophrenia, Schizoaffective, Tardive dyskinesia, Insulin resistance, Obesity | (Phase I&II), randomized | 60 | December 2002 completed April 2007 | Regional Mental Health Care London, St. Thomas, CA Queen's University, Kingston, CA Northwick Park Hospital, UK Northern Ontario Medical School, Thunder Bay, CA | NCT00401089 |
| Seasonal allergic rhinitis | (Phase II), randomized | 200 | May 2008 and ongoing | Edmonton, Alberta, CA | NCT00726401 |
| Upper respiratory tract infection | (Phase II), randomized | 75 | November 2005 completed April 2006 | Misericordia Child Health Clinic and Stollery Children's Hospital, Edmonton, CA | NCT00255307 |
| Upper respiratory tract infection | (Phase IV), randomized | 327 | June 2005 completed June 2007 | Two General Outpatient Clinics, Hong Kong, CN | NCT00887172 |
| Xerostomia | Phase IV, randomized | 100 | September 2007 completed December 2008 | Kyung Hee East-West Neo Medical Center, Seoul, KR | NCT00911768 |

*<http://clinicaltrials.gov>

ginseng research to succeed on the back of remarkable in vitro, in vivo and clinical results.

GINSENG INTERACTIONS, SIDE EFFECTS AND LIMITATIONS

As discussed in earlier sections, ginseng has the ability to interact directly and indirectly with various molecular targets and modulate their activity. Therefore, ginseng may also interact with other conventional drugs and result in serious side effects. Ginseng is generally considered to be a stimulant; therefore, care should be taken if an individual is using caffeine, pseudoephedrine or other stimulants (53). It has been reported that vitamin C can interact with and may increase the absorption of ginseng (54). Studies have also demonstrated that ginseng increases the activity of warfarin through various mechanisms. Therefore, ginseng should not be used by patients receiving oral anticoagulant and/or antiplatelet medications (55, 56). Phenelzine is commonly used as an antidepressant and anxiolytic. It has been reported that ginseng interacts with phenelzine and their simultaneous use may decrease blood concentrations of alcohol and warfarin, and may cause mania (53, 57). Ginseng has been reported to have an adverse interaction with amlodipine (58) and it can also interfere with digoxin pharmacodynamics (59). It is believed that ginseng may interact with opioids and in some cases

inhibits the analgesic effects of such drugs (60). Some of the possible interactions of ginseng with other conventional drugs are summarized in Table III.

Ginseng appears to be quite safe when properly used; however, high doses or long-term use may cause some adverse effects. Moreover, ginseng interaction with other drugs may also lead to side effects. Some of the commonly reported side effects include reactions such as nervousness, restlessness, excited feeling, trouble sleeping, gastrointestinal problems, headache, insomnia, anxiety, breast soreness or tenderness, skin rashes, asthma attacks, increased blood pressure, diarrhea, euphoria, skin eruptions, heart palpitations or postmenopausal uterine bleeding (61, 62). A study reported with some level of uncertainty that ginseng may intensify seizures (63). Some of the commonly observed side effects are summarized in Table III.

Ginseng (and other herbal medicines) is associated with other limitations and problems. Consistency in chemical composition and pharmacological properties is fundamental for the safe and effective use of herbal drugs; however, ginseng and other herbal products frequently fail to meet this standard. Ginseng extracts vary in composition depending on genetic variability, harvesting season, locality and other environmental factors (1, 4).

Table III. A summary of ginseng interactions with other drugs and side effects.

| Ginseng interactions/side effects | Reference |
|---|------------|
| <i>Drugs with which ginseng may interact</i> | |
| Amlodipine | 58 |
| Caffeine, pseudoephedrine or other stimulants | 53 |
| Digoxin | 59 |
| Opioids | 60 |
| Phenelzine | 58 |
| Vitamin C | 54 |
| Warfarin | 53, 55, 57 |
| <i>Ginseng side effects</i> | |
| Asthma attacks and diarrhea | 61, 62 |
| Breast soreness or tenderness | 61, 62 |
| Gastrointestinal problems | 61, 62 |
| Headache, insomnia and anxiety | 61, 62 |
| Increased blood pressure and heart palpitations | 61, 62 |
| Nervousness, restlessness and excited feeling | 61, 62 |
| Skin rashes and skin eruption | 61, 62 |

Poor extraction methods constitute another problem concerning ginseng and other herbal research. Chromatographic techniques and marker compounds are commonly used for the standardization of herbal products, but this does not guarantee consistent pharmacological activity or stability. In a study on ginseng preparations, the amount of ginsenosides varied from 11.9% to 327.7% of the label claim (64). Lack of standardization of ginseng preparations is another serious problem for researchers and thus they cannot rely on commercially available herbal products for their research studies. Despite the fact that unregulated and inappropriate use of ginseng may have serious side or toxic effects, based on laboratory and clinical studies it would be safe and effective if used in consultation with licensed and experienced herbalists or health specialists. Moreover, the use of high-quality and regulated brands of ginseng preparations may also ensure its safety and efficacy to a certain extent.

DISCLOSURES

The authors state no conflicts of interest.

REFERENCES

- Chang, Y.S., Seo, E.K., Gyllenhaal, C., Block, K.I. *Panax ginseng: A role in cancer therapy?* Integr Cancer Ther 2003, 2(1): 13-33.
- Lee, S.T., Chu, K., Sim, J.Y., Heo, J.H., Kim, M. *Panax ginseng enhances cognitive performance in Alzheimer disease.* Alzheimer Dis Assoc Disord 2008, 22(3): 222-6.
- Lee, F.C. *Facts About Ginseng, The Elixir of Life.* Elizabeth, New Jersey: Hollyn International Corporation, 1992.
- Jia, L., Zhao, Y. *Current evaluation of the millennium phytomedicine—Ginseng (I): Etymology, pharmacognosy, phytochemistry, market and regulations.* Curr Med Chem 2009, 16(19): 2475-84.
- Attele, A.S., Wu, J.A., Yuan, C.S. *Ginseng pharmacology: Multiple constituents and multiple actions.* Biochem Pharmacol 1999, 58(11): 1685-93.
- Wahid, F., Jung, H., Khan, T., Hwang, K.H., Kim, Y.Y. *Effects of red ginseng extract on visual sensitivity and ERG b-wave of bullfrog's eye.* Planta Med 2010, 76(5): 426-32.
- Jeong, C.S. *Effect of butanol fraction of Panax ginseng head on gastric lesion and ulcer.* Arch Pharm Res 2002, 25(1): 61-6.
- Jeong, C.S., Hyun, J.E., Kim, Y.S. *Ginsenoside Rb1: The anti-ulcer constituent from the head of Panax ginseng.* Arch Pharm Res 2003, 26(11): 906-11.
- Hashimoto, K., Satoh, K., Murata, P. et al. *Components of Panax ginseng that improve accelerated small intestinal transit.* J Ethnopharmacol 2003, 84(1): 115-9.
- Kim, H.J., Lee, Y.H., Kim, S.II. *Antihepatotoxic components of Korean ginseng: Effect on lipid peroxidation.* Korean Biochem J 1989, 22 (1): 12-8.
- Bai, C.X., Sunami, A., Namiki, T., Sawanobori, T., Furukawa, T. *Electrophysiological effects of ginseng and ginsenoside Re in guinea pig ventricular myocytes.* Eur J Pharmacol 2003, 476(1-2): 35-44.
- Wang, Z., Li, M., Wu, W.K., Tan, H.M., Geng, D.F. *Ginsenoside Rb1 preconditioning protects against myocardial infarction after regional ischemia and reperfusion by activation of phosphatidylinositol-3-kinase signal transduction.* Cardiovasc Drugs Ther 2008, 22(6): 443-52.
- Scaglione, F., Weiser, K., Alessandria, M. *Effects of the standardised ginseng extract G115 (Reg.) in patients with chronic bronchitis: A nonblinded, randomised, comparative pilot study.* Clin Drug Invest 2001, 21(1): 41-5.
- Song, Z., Johansen, H.K., Faber, V., Moser, C., Kharazmi, A., Rygaard, J., Hoiby, N. *Ginseng treatment reduces bacterial load and lung pathology in chronic Pseudomonas aeruginosa pneumonia in rats.* Antimicrob Agents Chemother 1997, 41(5): 961-4.
- Lam, S.K., Ng, T.B. *Isolation of a novel thermolabile heterodimeric ribonuclease with antifungal and antiproliferative activities from roots of the Sanchi Ginseng Panax notoginseng.* Biochem Biophys Res Commun 2001, 285(2): 419-23.
- Sung, W.S., Lee, D.G. *In vitro candidacidal action of Korean red ginseng saponins against Candida albicans.* Biol Pharm Bull 2008, 31(1): 139-42.
- Singh, V.K., George, C.X., Singh, N., Agarwal, S.S., Gupta, B.M. *Combined treatment of mice with Panax ginseng extract and interferon inducer. Amplification of host resistance to Semliki forest virus.* Planta Med 1983, 47(4): 234-6.
- Ng, T.B., Wang, H. *Panaxagin, a new protein from Chinese ginseng possesses anti-fungal, anti-viral, translation-inhibiting and ribonuclease activities.* Life Sci 2001, 68(7): 739-49.
- Wu, C.Y., Jan, J.T., Ma, S.H. et al. *Small molecules targeting severe acute respiratory syndrome human coronavirus.* Proc Natl Acad Sci U S A 2004, 101(27): 10012-7.
- Cho, Y.K., Sung, H., Lee, H.J., Joo, C.H., Cho, G.J. *Long-term intake of Korean red ginseng in HIV-1-infected patients: Development of resistance mutation to zidovudine is delayed.* Int Immunopharmacol 2001, 1(7): 1295-305.
- Park, W.S., Shin, D.Y., Kim, do. R., Yang, W.M., Chang, M.S., Park, S.K. *Korean ginseng induces spermatogenesis in rats through the activation of cAMP-responsive element modulator (CREM).* Fertil Steril 2007, 88(4): 1000-2.
- Jang, D.J., Lee, M.S., Shin, B.C., Lee, Y.C., Ernst, E. *Red ginseng for treating erectile dysfunction: A systematic review.* Br J Clin Pharmacol 2008, 66(4): 444-50.
- Ryu, J.K., Lee, T., Kim, D.J. et al. *Free radical-scavenging activity of Korean red ginseng for erectile dysfunction in non-insulin-dependent diabetes mellitus rats.* Urology 2005, 65(3): 611-5.
- Salvati, G., Genovesi, G., Marcellini, L., Paolini, P., De, Nuccio. I., Pepe, M., Re, M. *Effects of Panax ginseng C.A. Meyer saponins on male fertility.* Panminerva Med 1996, 38(4): 249-54.

25. Yin, J., Zhang, H., Ye, J. *Traditional Chinese medicine in treatment of metabolic syndrome*. *Endocr Metab Immune Disord Drug Targets* 2008, 8(2): 99-111.
26. Attele, A.S., Zhou, Y.P., Xie, J.T. et al. *Antidiabetic effects of Panax ginseng berry extract and the identification of an effective component*. *Diabetes* 2002, 51(6): 1851-8.
27. Xie, J.T., Zhou, Y.P., Dey, L. et al. *Ginseng berry reduces blood glucose and body weight in db/db mice*. *Phytomedicine* 2002, 9(3): 254-8.
28. Dey, L., Xie, J.T., Wang, A., Wu, J., Maleckar, S.A., Yuan, C.S. *Anti-hyperglycemic effects of ginseng: Comparison between root and berry*. *Phytomedicine* 2003, 10(6-7): 600-5.
29. Xie, J.T., Mehendale, S.R., Wang, A., Han, A.H., Wu, J.A., Osinski, J., Yuan, C.S. *American ginseng leaf: Ginsenoside analysis and hypoglycemic activity*. *Pharmacol Res* 2004, 49(2): 113-7.
30. Park, J., Cho, J.Y. *Anti-inflammatory effects of ginsenosides from Panax ginseng and their structural analogs*. *Afr J Biotechnol* 2009, 8(16): 3682-90.
31. Lee, J.H., Lee, J.H., Lee, Y.M., Kim, P.N., Jeong, C.S. *Potential analgesic and anti-inflammatory activities of Panax ginseng head butanolic fraction in animals*. *Food Chem Toxicol* 2008, 46(12): 3749-52.
32. Jung, S.H., Woo, M.S., Kim, S.Y. et al. *Ginseng saponin metabolite suppresses phorbol ester-induced matrix metalloproteinase-9 expression through inhibition of activator protein-1 and mitogen-activated protein kinase signaling pathways in human astrogloma cells*. *Int J Cancer* 2006, 118(2): 490-7.
33. Xiang, Y.Z., Shang, H.C., Gao, X.M., Zhang, B.L. *A comparison of the ancient use of ginseng in traditional Chinese medicine with modern pharmacological experiments and clinical trials*. *Phytother Res* 2008, 22(7): 851-8.
34. Hofseth, L.J., Wargovich, M.J. *Inflammation, cancer, and targets of ginseng*. *J Nutr* 2007, 137(1, Suppl.): 183S-5S.
35. Varjas, T., Nowrasteh, G., Budan, F. et al. *Chemopreventive effect of Panax ginseng*. *Phytother Res* 2009, 23 (10): 1399-403.
36. Kang, K.A., Kim, Y.W., Kim, S.U. et al. *G1 phase arrest of the cell cycle by a ginseng metabolite, compound K, in U937 human monocytic leukemia cells*. *Arch Pharm Res* 2005, 28(6): 685-90.
37. Manna, F., Abdel-Wahhab, M.A., Ahmed, H.H., Park, M.H. *Protective role of Panax ginseng extract standardized with ginsenoside Rg3 against acrylamide-induced neurotoxicity in rats*. *J Appl Toxicol* 2006, 26(3): 198-206.
38. Kim, H.S., Kim, K.S. *Inhibitory effects of ginseng total saponin on nicotine-induced hyperactivity, reverse tolerance and dopamine receptor supersensitivity*. *Behav Brain Res* 1999, 103(1): 55-61.
39. Peralta, E.A., Murphy, L.L., Minnis, J., Louis, S., Dunnington, G.L. *American ginseng inhibits induced COX-2 and NFkB activation in breast cancer cells*. *J Surg Res* 2009, 157(2): 261-7.
40. Ichikawa, T., Li, J., Nagarkatti, P., Nagarkatti, M., Hofseth, L.J., Windust, A., Cui, T. *American ginseng preferentially suppresses STAT/iNOS signaling in activated macrophages*. *J Ethnopharmacol* 2009, 125(1): 145-50.
41. Kimura, Y., Sumiyoshi, M., Kawahira, K., Sakanaka, M. *Effects of ginseng saponins isolated from red ginseng roots on burn wound healing in mice*. *Br J Pharmacol* 2006, 148(6): 860-70.
42. Cho, S.W., Cho, E.H., Choi, S.Y. *Ginsenosides activate DNA polymerase delta from bovine placenta*. *Life Sci* 1995, 57(14): 1359-65.
43. Friedl, R., Moeslinger, T., Kopp, B., Spieckermann, P.G. *Stimulation of nitric oxide synthesis by the aqueous extract of Panax ginseng root in RAW 264.7 cells*. *Br J Pharmacol* 2001, 134(8): 1663-70.
44. Luo, J.Z., Luo, L. *American ginseng stimulates insulin production and prevents apoptosis through regulation of uncoupling protein-2 in cultured beta cells*. *Evid Based Complement Alternat Med* 2006, 3(3): 365-72.
45. Songa, Z., Mosera, C., Wua, H., Faberb, V., Kharazmia, A., Hoibya, N. *Cytokine modulating effect of ginseng treatment in a mouse model of Pseudomonas aeruginosa lung infection*. *J Cyst Fibros* 2003, 2(3): 112-9.
46. Jeong, S.M., Lee, J.H., Kim, J.H. et al. *Stereospecificity of ginsenoside Rg3 action on ion channels*. *Mol Cells* 2004, 18(3): 383-9.
47. Choi, S.E., Choi, S., Lee, J.H., Whiting, P.J., Lee, S.M., Nah, S.Y. *Effects of ginsenosides on GABA(A) receptor channels expressed in Xenopus oocytes*. *Arch Pharm Res* 2003, 26(1): 28-33.
48. Choi, S., Lee, J.H., Oh, S., Rhim, H., Lee, S.M., Nah, S.Y. *Effects of ginsenoside Rg2 on the 5-HT3A receptor-mediated ion current in Xenopus oocytes*. *Mol Cells* 2003, 15(1): 108-13.
49. Barton, D.L., Soori, G.S., Bauer, B.A. et al. *Pilot study of Panax quinquefolius (American ginseng) to improve cancer-related fatigue: A randomized, double-blind, dose-finding evaluation: NCCTG trial N03CA*. *Support Care Cancer* 2010, 18(2): 179-87.
50. Bahrke, M.S., Morgan, W.R. *Evaluation of the ergogenic properties of ginseng: An update*. *Sports Med* 2000, 29(2): 113-33.
51. Scaglione, F., Ferrara, F., Dugnani, S., Falchi, M., Santoro, G., Fraschini, F. *Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer*. *Drugs Exp Clin Res* 1990, 16(10): 537-42.
52. Sotaniemi, E.A., Haapakoski, E., Rautio, A. *Ginseng therapy in non-insulin-dependent diabetic patients*. *Diabetes Care* 1995, 18(10): 1373-5.
53. Izzo, A.A., Ernst, E. *Interactions between herbal medicines and prescribed drugs: An updated systematic review*. *Drugs* 2009, 69(13): 1777-98.
54. Li, J.P., Huang, M., Teoh, H., Man, R.Y. *Interactions between Panax quinquefolium saponins and vitamin C are observed in vitro*. *Mol Cell Biochem* 2000, 204(1-2): 77-82.
55. Argento, A., Tiraferri, E., Marzalani, M. *Oral anticoagulants and medicinal plants. An emerging interaction*. *Ann Ital Med Int* 2000, 15(2): 139-43.
56. Heck, A.M., DeWitt, B.A., Lukes, A.L. *Potential interactions between alternative therapies and warfarin*. *Am J Health Syst Pharm* 2000, 57(13): 1221-7; quiz 1228-30.
57. Izzo, A.A., Ernst, E. *Interactions between herbal medicines and prescribed drugs: A systematic review*. *Drugs* 2001, 61(15): 2163-75.
58. Dergal, J.M., Gold, J.L., Laxer, D.A. et al. *Potential interactions between herbal medicines and conventional drug therapies used by older adults attending a memory clinic*. *Drugs Aging* 2002, 19(11): 879-86.
59. Miller, L.G. *Herbal medicinals: Selected clinical considerations focusing on known or potential drug-herb interactions*. *Arch Intern Med* 1998, 158(20): 2200-11.
60. Abebe, W. *Herbal medication: Potential for adverse interactions with analgesic drugs*. *J Clin Pharm Ther* 2002, 27(6): 391-401.
61. Boniel, T., Dannon, P. *The safety of herbal medicines in the psychiatric practice*. *Harefuah* 2001, 140(8): 780-3, 805.
62. Spinella, M. *Herbal medicines and epilepsy: The potential for benefit and adverse effects*. *Epilepsy Behav* 2001, 2(6): 524-32.
63. Jeon, B.H., Kim, C.S., Park, K.S. et al. *Effect of Korea red ginseng on the blood pressure in conscious hypertensive rats*. *Gen Pharmacol* 2000, 35(3): 135-41.
64. Straus, S.E. *Herbal medicines—What's in the bottle?* *N Engl J Med* 2002, 347(25): 1997-8.
65. Seo, J.J., Lee, J.W., Lee, W.K., Hong, J.T., Lee, C.K., Lee, M.K., Oh, K.W. *Inhibitory effects of ginseng total saponin on up-regulation of cAMP pathway induced by repeated administration of morphine*. *Arch Pharm Res* 2008, 31(2): 167-70.
66. Park, M.Y., Lee, K.S., Sung, M.K. *Effects of dietary mulberry, Korean red ginseng, and banaba on glucose homeostasis in relation to PPAR-alpha*.

- PPAR-gamma, and LPL mRNA expressions. *Life Sci* 2005, 77(26): 3344-54.
67. Chen, D., Zuo, G., Li, C. et al. Total saponins of *Panax ginseng* (TSPG) promote erythroid differentiation of human CD34+ cells via EpoR-mediated JAK2/STAT5 signaling pathway. *J Ethnopharmacol* 2009, 126(2): 215-20.
 68. Lu, M.C., Lai, T.Y., Hwang, J.M. et al. Proliferation- and migration-enhancing effects of ginseng and ginsenoside Rg1 through IGF-I and FGF-2-signaling pathways on RSC96 Schwann cells. *Cell Biochem Funct* 2009, 27(4): 186-92.
 69. Chang, H.F., Lin, Y.H., Chu, C.C., Wu, S.J., Tsai, Y.H., Chao, J.C. Protective effects of *Ginkgo biloba*, *Panax ginseng*, and *Schizandra chinensis* extract on liver injury in rats. *Am J Chin Med* 2007, 35(6): 995-1009.
 70. Yue, P.Y., Mak, N.K., Cheng, Y.K. et al. Pharmacogenomics and the Yin/Yang actions of ginseng: Anti-tumor, angiomodulating and steroid-like activities of ginsenosides. *Chin Med* 2007, 2: 6.
 71. Morisaki, N., Watanabe, S., Tezuka, M. et al. Mechanism of angiogenic effects of saponin from ginseng *Radix rubra* in human umbilical vein endothelial cells. *Br J Pharmacol* 1995, 115(7): 1188-93.
 72. Liao, B., Newmark, H., Zhou, R. Neuroprotective effects of ginseng total saponin and ginsenosides Rb1 and Rg1 on spinal cord neurons in vitro. *Exp Neurol* 2002, 173(2): 224-34.
 73. Voces, J., Alvarez, A.I., Vila, L., Ferrando, A., Cabral de Oliveira, C., Prieto, J.G. Effects of administration of the standardized *Panax ginseng* extract G115 on hepatic antioxidant function after exhaustive exercise. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* 1999, 123(2): 175-84.
 74. Gum, S.I., Jo, S.J., Ahn, S.H., Kim, S.G., Kim, J.T., Shin, H.M., Cho, M.K. The potent protective effect of wild ginseng (*Panax ginseng* C.A. Meyer) against benzo[alpha]pyrene-induced toxicity through metabolic regulation of CYP1A1 and GSTs. *J Ethnopharmacol* 2007, 112(3): 568-76.
 75. Kim, N.D., Pokharel, Y.R., Kang, K.W. Ginsenoside Rd enhances glutathione levels in H4IIE cells via NF- κ B-dependent γ -glutamylcysteine ligase induction. *Pharmazie* 2007, 62(12): 933-6.
 76. Lee, S.H., Jung, B.H., Kim, S.Y., Lee, E.H., Chung, B.C. The antistress effect of ginseng total saponin and ginsenoside Rg3 and Rb1 evaluated by brain polyamine level under immobilization stress. *Pharmacol Res* 2006, 54(1): 46-9.
 77. Park, S.E., Park, C., Kim, S.H. et al. Korean red ginseng extract induces apoptosis and decreases telomerase activity in human leukemia cells. *J Ethnopharmacol* 2009, 121(2): 304-12.
 78. Wang, Y., Ye, X., Ma, Z. et al. Induction of cytochrome P450 1A1 expression by ginsenoside Rg1 and Rb1 in HepG2 cells. *Eur J Pharmacol* 2008, 601(1-3): 73-8.
 79. Oh, S.H., Yin, H.Q., Lee, B.H. Role of the Fas/Fas ligand death receptor pathway in ginseng saponin metabolite-induced apoptosis in HepG2 cells. *Arch Pharm Res* 2004, 27(4): 402-6.
 80. Choi, S. Epidermis proliferative effect of the *Panax ginseng* ginsenoside Rb2. *Arch Pharm Res* 2002, 25(1): 71-6.
 81. Tachikawa, E., Kudo, K., Harada, K., Kashimoto, T., Miyate, Y., Kakizaki, A., Takahashi, E. Effects of ginseng saponins on responses induced by various receptor stimuli. *Eur J Pharmacol* 1999, 369(1): 23-32.
 82. Lee, J.H., Jeong, S.M., Lee, B.H. et al. Effect of calmodulin on ginseng saponin-induced Ca²⁺-activated Cl⁻ channel activation in *Xenopus laevis* oocytes. *Arch Pharm Res* 2005, 28(4): 413-20.
 83. Yeo, M., Kim, D.K., Cho, S.W., Hong, H.D. Ginseng, the root of *Panax ginseng* C.A. Meyer, protects ethanol-induced gastric damages in rat through the induction of cytoprotective heat-shock protein 27. *Dig Dis Sci* 2008, 53(3): 606-13.