Review Article

An Overview on Panax ginseng

Jai Narayan Mishra* and Navneet Kumar Verma

Department of Pharmacy, Kailash Institute of Pharmacy and Management, GIDA, Gorakhpur -273209, Uttar Pradesh, India.

ABSTRACT

The origin of ginseng dates back to prehistory. In China, Shennong also known as Emperor Yan, the Yellow Emperor, or one of the"Three Emperors"(the Emperor who is said to have started herbal medicine about 5,500 years ago) is reported to have tasted hundreds of plants to discover many medicinal herbs. For many many years, mankind has been using various plants as nutrient, beverage, cosmetics, dye and medicine to maintain health and to improve quality of life. In Asia, particularly, *Panax ginseng* C.A. Meyer is considered to be the most precious plant among herbs, and ginseng has been in the spotlight worldwide. Even in the Western world, where there are greatly advanced research facilities and highly qualified man-power available, and are regarded to be capable of conquering any hard-to-cure ailments, many people has recently been reported to use herbal medicine, particularly ginseng. In the present compilation of papers, many scientists contributed papers pertaining to"Chemopreventive effects of ginseng". In order to facilitate the readers understand easier and better, I catalogued this collection as follows: The spiritual nature of ginseng in the Far East, the history of ginseng, nomenclature and geographical distribution of ginseng, and type of ginseng products.

Keywords: *Ginseng; Chemoprevention; Panax ginseng C.A. Meyer.*

INTRODUCTION

Ginseng refers to the root of several species in the plant genus *Panax* (C. A. Meyer Araliaceae). Among them, *Panax ginseng* is the most widely used ginseng and is indigenous to the Far East countries (most notably China and Korea). *Panax ginseng* was first cultivated around 11 BC and has a medical history of more than five thousand years. The genus name of *Panax ginseng* "Panax" was given by the Russian botanist, C.A. Meyer, and is derived from the Greek words "pan" meaning all and "axos" meaning cure. The species name "ginseng" comes from the Chinese word "rensheng" which means "human" as ginseng root resemble the human body [1]. In China, ginseng roots are harvested when the plant is 3-6 years old and then, the roots are submitted to air drying (white ginseng) or are steamed (red ginseng). Interestingly, after these two ways of treatment the roots differ in their content of saponins [1] and this may be the reason for the variable actions of different ginseng products. Other species of the genus *Panax* include *Panax quinquefolius* (found in southern Canada and in the United States), *Panax japonicus* (grown in Japan), and less frequently *Panax notoginseng* (grown in China), *Panax pseudoginseng* (grown in Nepal and eastern Himalayas) and *Panax vietnamensis* (grown in Vietnam) [2]. Ginseng is a widespread herbal medicine [3] and it has served as an important component of many Chinese prescriptions for thousands of years [4, 5]. Today it still occupies a permanent and prominent position in the herbal (best-sellers) list and is considered the most widely taken herbal product in the world [6]. Moreover, it is estimated that more than six million Americans are regularly consuming ginseng products [7]. They do not only believe that ginseng will engender physical benefits, but that it will also have positive effect on their cognitive performance and well-being. Ginsenosides or ginseng saponins are the principle active ingredients in ginseng and more than thirty different ginsenosides have been identified [8, 9]. Ginsenosides are unique to *Panax* species, many of which exist in minute amounts and are believed to be responsible for most of ginseng's actions [10-13]. Addition-ally, ginsenosides operate by many mechanisms of action and it was suggested that each ginsenoside may have its own specific tissue-dependent effects [14]. The basic structure of ginsenosides is similar. They consist of a gonane steroid nucleus with 17 carbon atoms arranged in four rings. The

characteristic biological responses for each ginsenosides are attributed to the differences in the type, position and number of sugar moieties attached by glycosidic bond at C-3 and C-6 [15]. Based on their structural differences, they can be classified into three categories: the panaxadiol group (e.g. Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1), the panaxatriol group (e.g. Re, Rf, Rg1, Rg2, Rh1), and the oleanolic acid group (e.g. Ro) [5, 16]. Interestingly, the ginsenoside content of ginseng can vary depending on the *Panax* species, the plant age, the part of the plant, the preservation method, the season of harvest and the ex-traction method [17, 18].

Table1: Scientific Classification

Kingdom:	Plantae
(unranked):	Angiosperms
(unranked):	Eudicots
(unranked):	Asterids
Order:	Apiales
Family:	Araliaceae
Genus:	*Panax*
Species:	*Panax ginseng*

Fig. 1: *Panax ginseng*

Active Constituents

Panax ginseng contains triterpene glycosides, or saponins, commonly referred to as ginsenosides. Many active compounds can be found in all parts of the plant, including amino acids, alkaloids, phenols, proteins, polypeptides, and vitamins B1 and B2.3 Up to 40 distinct ginsenosides have been identified by thin layer chromatography (TLC) and methanol extraction experiments. The nomenclature of ginsenosides is by the designation Rx, where x represents the retention factor (Rf) value from the sequence of spots on TLC from bottom to top. The two major sub-types of ginsenosides, protopanaxadiol and protopanaxatriol, are classified according to the arrangement and number of sugar residues – glucose, rhamnose, xylose, and arabinose – on the ginsenosides. Rb1, Rb2, Rc, and Rd are examples of protopanaxadiol ginsenosides. Re, Rf, Rg1, and Rg2 are examples of protopanaxatriols. [19-24] These ginsenosides have varying concentrations in red and white Panax ginseng extracts due to different processing method that affect deacetylating enzymes within the raw plant material.[25]

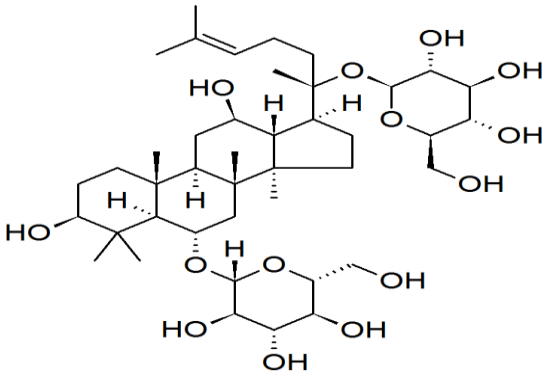

Fig. 2: Ginsenosides

Pharmacokinetics

Recent research supports the hypothesis that ginsenosides are activated by intestinal bacteria through deglycosylation and esterification. Protopanaxadiol and protopanaxatriol glycosides are absorbed into the blood or lymph and transported to target tissues for esterification with stearic, oleic, or palmitic fatty acids. The transformation into ginsenoside metabolites, M1 (20S-protopanaxadiol 20-O-B-D-glucopyranoside) and M4 (20S-protopanaxatriol) affect excretion and utilization of the metabolites.[26]

Mechanism of Action

Panax ginseng is often referred to as an adaptogen, which suggests it has varied actions and effects on the body that support nonspecific resistance to biochemical and physical stressors, improve vitality and longevity, and enhance mental capacity. [20,27,28] Reviews suggest Panax ginseng has immunomodulating activity by affecting the hypothalamic-pituitary-adrenal (HPA) axis.3,11In vitro experiments reveal enhanced natural killer (NK) cell activity and increased immune cell phagocytosis after ginsenoside exposure.[20] According to a 1999 World Health Organization review, ginseng saponins “are thought to decrease serum prolactin, thereby increasing libido” in male impotence.[29]

Clinical Indications

Panax ginseng has been widely studied in double-blind, randomized, placebo-controlled trials (RCTs). Although ginseng has been used by Asian cultures for thousands of years for conditions such as fatigue, mental stress, blood sugar regulation, improving libido, and supporting longevity, modern clinical studies have focused on the use of Panax ginsengin cancer prevention, blood sugar regulation, fatigue, and immunomodulation in human health and disease.

Immune Modulation

A double-blind, placebo-controlled eight-week study examined the immune effects of 100 mg Ginsana (G115), 100 mg liquid ginseng extract, or placebo twice daily in 60 healthy volunteers. Blood samples collected at baseline, week four, and week eight examined polymorphonuclear (PMN) cell chemotaxis, phagocytosis, total lymphocytes, T-helper and T-suppressor cells, and NK-cell activity. The groups receiving ginseng experienced consistent improvement in immune system activity at week four and statistically significant Differences at week eight, evidenced by improvements in PMN cell chemotaxis, phagocytosis, and total number of T-helper and T-suppressor cells. The authors concluded ginseng extract stimulates the immune system and the standardized extract is more effective than the liquid ginseng extract.[30] Some of the same researchers examined the effects of Panax ginseng extract on the immune response to vaccination. The multicenter, 12-week, double-blind RCT compared immune response in 227 participants, measured as NK-cell activity, at weeks eight and 12, post influenza vaccine given at week four. The treatment group received 100 mg G115 twice daily. NK-cell activity for the ginseng group was double that of the placebo group ($p<0.0001$) at weeks eight and 12. Serum antibody titers were 272 units in the ginseng group compared to 171 units in the placebo group. A significant decrease in the frequency of upper respiratory infections during weeks 4-12 was noted in the treatment group compared to placebo; 15 cases versus 42 cases, respectively. This study supports the role of ginseng in immune system modulation. [31] An RCT compared the effects of red Panax ginseng on HIV-1 infected patients (n=61).[32] The purpose of this study was to determine the effects of red Panax ginseng after accounting for HLA type (I or II and class A, B, and C), on CD4 counts, CD8 counts, and the trend toward decreased resistance to anti-Retroviral drugs. HLA type can be associated with an improved prognosis in HIV patients, based on an algorithm that also predicts risk of disease progression.[33] The treatment group received 5.4 g red Panax ginseng daily. Blood samples were taken from the control group (n=199) and HIV-1 infected patients every six months throughout the study. Data analysis revealed an inverse correlation between the HLA score and the decrease of CD4 T cells over time, a decrease in the decline of CD4 T cells associated with the intake of red Panax ginseng, and a significant ($p<0.05$) decline of CD4 T cells, independent of the HLA class I effects on immune system cells. The authors concluded that red Panax ginseng and HLA type independently affect the slow depletion of CD4 T cells in HIV-infected patients.

Diabetes

Eclectic medicine texts reference Panax ginseng for its beneficial use in blood sugar regulation. [19,34] In a double-blind RCT, Sotaniemi et al examined the efficacy of Panax ginsengin newly diagnosed type 2 diabetics.[24] Parameters measured included physical performance, mood, serum lipids, fasting blood glucose, hemoglobin A1c (HbA1c), amino terminal propeptide (PIIINP) concentration, and body weight. PIIINP serum levels are associated with coronary artery disease and were used as a safety parameter in this study. The study participants (n=36) were given 100 mg ginseng extract, 200 mg ginseng extract, or placebo daily for eight weeks. Compared to the placebo group, the 200-mg ginseng group experienced elevated mood, improved physical performance, and reduced fasting blood glucose. The authors concluded ginseng warrants further study as an adjuvant to diabetes management. A 2005 double-blind, crossover RCT examined the effects of Panax ginseng on blood glucose levels and cognitive performance during sustained mental activity.[35] Healthy young adults (n=30) took a 10-minute test battery for baseline results, then were given 200 mg G115, 400 mg G115, or placebo. One hour later the test battery was repeated six times in rapid succession. Blood sugar levels were assessed at baseline and twice during the testing procedure. The 200-mg and 400-mg G115 doses reduced blood glucose levels significantly ($p<0.005$). Significant improvement was also noted in the ability to complete the serial sevens subtraction task after taking 200 mg G115 ($p<0.05$). The authors

concluded Panax ginseng improves mental performance, possibly by regulating glucose metabolism. A double-blind, 12-week RCT examined the effect of red Panax ginseng on HbA1c levels in 19 subjects with well-controlled type 2 diabetes.[36] Study participants received 2 g ginseng or placebo three times daily before meals. Plasma glucose and insulin, insulin sensitivity, and oral glucose tolerance were secondary measures of efficacy, while blood pressure checks and liver and kidney function tests assessed safety. Although no change was seen in HbA1c levels with ginseng, the participants remained well controlled throughout the study without pharmaceutical intervention – with average levels of HbA1c of 6.5 percent. A significant 8- to 11-percent decrease in glucose on the oral glucose tolerance test and 33-percent decrease in plasma insulin ($p<0.05$) was seen in the ginseng group compared to placebo. No change was reported in safety parameters throughout the study, which led the authors to conclude red Panax ginseng is safe to use in the treatment of type II diabetes.

Cancer Prevention

Numerous in vitro and animal studies have examined the interaction of Panax ginseng with carcinogenesis, apoptosis, angiogenesis, and metastasis.[24,37-40] A recent paper proposed an anti-inflammatory role of Panax ginseng in the sequence of progression to promotion in a model of carcinogenesis.[41] Panax ginseng affects multiple points within the inflammatory cascade, including inhibition of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and nuclear factor kappa B (NF-κB).[42,43] In a review, Lee et al concluded Panax ginseng has a radio protective effect associated with antioxidant and immune-modulation properties.8An epidemiological study examined the protective effect of a variety of Panax ginseng products on 3,974 patients with different types of cancer compared to case-matched controls for 67 weeks.[44] Patients taking ginseng demonstrated a 50-percent lower risk of cancer recurrence compared to patients not taking ginseng. Red ginseng offered greater protection than white ginseng. Cancer incidence decreased by 36- and 69 percent in subjects taking ginseng for one year or five years, respectively. A greater protective effect was seen in cancers of the lip, esophagus, pharynx, lung, and liver. A prospective study examined non-organ specific cancer prevention of Panax ginseng.[45] This cohort study used case-controlled matches (n=4,587) of Koreans over age 40. A questionnaire was used to determine pattern of ginseng intake, initial age of ginseng intake, frequency, duration, and form of ginseng (fresh, dried, etc.) used by study participants. Ginseng intake correlated with a 60-percent reduction in cancer incidence, with a direct dose-response relationship. Drug-Botanical Interactions According to a review by Blumenthal et al, there are no known interactions between Panax ginseng and pharmaceuticals, as reported by the German Commission E.[20,46] Caution is advised with concomitant use with phenelzine, coumadin, oral hypoglycemics, insulin, and caffeine, based on preclinical studies and proposed mechanisms of action.[28,47] A recent review by Seely et al suggests cautious use of Panax ginseng in pregnancy and lactation, although no specific teratogenic or hormone-disrupting activity was noted.[22]

Side Effects and Toxicity

Panax ginseng is associated with low toxicity; few adverse events have been reported with proper us-age. Adverse events have been associated with high doses and long-term usage, producing what has been cited in the literature as ginseng abuse syndrome,[22,28] although case studies associated with ginseng abuse syndrome have been discounted by several authors.[20] Side effects such as hypertension, nausea, diarrhea, headache, mastalgia, insomnia, and skin rash have been noted.[19,22,28]

Dosage

Ginseng root can be chewed, or taken as a powder, liquid extract, decoction, or infusion. The level of ginsenosides can vary depending on steeping time and type of preparation. The ginsenoside concentration can vary from approximately 64-77 percent. Crude preparations of 1-2 g dried root powder can be taken daily for up to three months, according to recommendations by the German Commission E.29 A decoction can be prepared by simmering 3-9 g dried root in 720-960 mL (24-32 oz) water for 45 minutes. A fluid extract (1:2 concentration) prepared from crude root can be dosed at 1-6 mL daily.31An infusion can be made by pouring 150-250 mL (5-8 oz) of boiling water over 1-2 g root, steeping for 10 minutes covered, and then straining before drinking. Dosage of Panax ginseng extract standardized to 4-percent ginsenosides is 200 mg per day, in divided

doses, yielding 8 mg ginsenosides daily. Other reports suggest significantly higher doses of 80-240 mg ginsenosides daily might be warranted in some cases. [20]

Warnings and Contraindications

The German Commission E and the World Health Organization report no known contraindications for Panax ginseng.[20, 29] Caution is advised during pregnancy and lactation due to a lack of controlled human clinical studies.[20,22] Teratogenicity has been documented in an in vitro rat embryo model, but the implication for human health is questionable due to dosages used that exceed possible human consumption.[49] In Asian countries the use of Panax ginseng in TCM formulas is common throughout pregnancy and lactation.[22]

TYPES OF GINSENG PRODUCTS

The conventional sun-drying of ginseng was switched to the steaming method to meet the great demand for ginseng which was stimulated by active trade with China during the reign of King Ae, the 14th King of Balhae. Xu-Jing of the Sung Dynasty, an attendant to a special envoy of the Chinese Emperor to Korea, wrote in"Kaoli T'suching"of the impression of his visit to the (Korean) Kingdom of Koryo in 1123, during the reign of King In Jong. He described in his book that there were two kinds of ginseng products in Koryo, sun-dried and steamed ginseng; red ginseng [50]. *Panax ginseng* C.A. Meyer cultivated in Korea (Korean ginseng) is harvested after 4 to 6 yr of cultivation, and it is classified into three types depending on how it is processed:

(a) fresh ginseng (less than 4 yr old; can be consumed in its fresh state);

(b) white ginseng (4-6 yr old; dried after peeling); and

(c) red ginseng (harvested when 6 yr old, and then steamed and dried).

Each type of ginseng is further subcategorized as ginseng products; fresh sliced, juice, extract (tincture or boiled extract), powder, tea, tablet, capsule, etc. Two years old fresh ginseng is also used as an ingredient in the Korean chicken-ginseng soup known as "Samketang".

CONCLUSION

The pharmacologically active ingredients of ginseng are ginsenosides (ginseng saponins). In the current time, there is increasing evidence in the literature on the pharmacological and physiological actions of ginseng. Ginseng had been used primarily as a tonic to invigorate week bodies and help the restoration of homeostasis. However current in vivo and in vitro studies have shown its beneficial effects in a wide range of pathological conditions such as cardiovascular diseases, cancer, immune deficiency and hepatotoxicity. Moreover, recent research has suggested that some of ginseng's active ingredients also exert beneficial actions on aging, CNS disorders and neurodegenerative diseases. In general, antioxidant, anti-inflammatory, antiapoptotic and immunostimulant activities are mostly underlying the possible ginseng mediated protective mechanisms.

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