Review Article

PANAX GINSENG A DIVINE CHINESE HERB

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ABSTRACT

The *Panax* family araliceae consist of nine species, including *Panax ginseng*. *Panax ginseng* grows in the Northern hemisphere typically in cooler climates. Roots of Panax ginseng have various pharmacological activity such as antiallergic rhinitis activity, estrogenic activity, antiulcer activity, antidiabetic activity, antioxidant activity, immune enhancement activity, anticancer activity, antihyperglycemic activity, anxiolytic activity analgesic activity, cardiovascular activity, calcium channel inhibitory activity due to the presence of Ginsenoside-Rg_1, Rg_3, Re, Rd, Rb_1, Rb_2, Rc, 20(S)-Protopanaxadiol and 20(S) Protopanaxtriol.

Keywords: *Panax ginseng*, Pharmacological activity, Ginsenoside.

INTRODUCTION

The Panax family araliaceae consists of at least nine species, including *Panax ginseng*, *Panax quinquefolium* (*Xiyangshen*, American ginseng), *Panax notoginseng* (*Sanqi*) and *Panax japonicus* (Japanese ginseng).[1-3] Ginseng grows in the Northern Hemisphere, typically in cooler climates. They are slow growing perennial plants with fleshy roots. The plant grows 6 to 18 inches tall. The fruit is a pea-sized, globular to reniform, scarlet, smooth and glossy drupe, which contains 2 seeds. The plant usually bears three leaves, each with three to five leaflets 2 to 5 inches long.[4] In China, Korea, Japan and Russia, the cultivated ginseng roots are harvested when the plant is 3–6-year old. It should be noted that ginseng is not derived from the rhizomes (the thick stem that lies flat along the ground with roots and leaves growing from it).[4] The common names of *Panax ginseng* are American ginseng, Asiatic ginseng, Chinese ginseng, Five fingers, Japanese ginseng, Jintsam, Korean ginseng, Ninjin, Oriental ginseng, Schinsent, Seng and Sang, Tartar root, Western ginseng, Ginseng, Ginseng Asiatique, Ginseng Radix Alba, Ginseng Root, Guigai, Hong Shen, Japanese Ginseng, Jen-Shen, Jinsao, Jintsam, Insam, Korean Panax, Korean Panax Ginseng, Korean Red Ginseng, Korean White Ginseng, Oriental Ginseng, Radix Ginseng Rubra, Red Chinese Ginseng, Red Ginseng, Red Kirin Ginseng, Red Korean Ginseng, Red Panax Ginseng, Renshen, Renxian, Sheng Shai Shen, White Ginseng, White Panax Ginseng.[5-10] Ginseng root has been utilized for thousands of years in China, Korea and Japan as an important drug in Chinese medicine**.** *Panax ginseng* is commonly used either by itself or in combination with other medicinal ingredients. Panax meaning "all-healing" first coined by the Russian botanist Carl A. Meyer.[2,3] In traditional Chinese medicine (TCM) ginseng is a highly valued herb and has been applied to a variety of pathological conditions and illnesses such as hypodynamia, anorexia, shortness of breath, palpitation, insomnia, impotence, hemorrhage**.**[11]

PHARMACOLOGICAL ACTIVITIES OF EXTRACTS

Antiallergic rhinitis activity

Allergic rhinitis is clinically defined as a disorder of the nose induced by IgE mediated inflammation after allergen exposure of the nasal mucosa. Many reports have stated that *Panax ginseng* and fermented red ginseng have anti-inflammatory effects, especially against Th_2-type inflammation. This study was conducted to evaluate the therapeutic effects of fermented red ginseng in allergic rhinitis. In this 4-week, double-blind, placebo-controlled studies, 59 patients with persistent perennial allergic rhinitis were randomly divided into two groups: those receiving fermented red ginseng tablets (experimental group) and those receiving placebo (control group). The primary efficacy variable was the total nasal symptom score (TNSS; rhinorrhea, sneezing, itchy nose and nasal congestion). Secondary efficacy variables were the Rhinitis Quality of Life (RQoL) score and skin reactivity to inhalant allergens, as determined by the skin prick test. There was no significant difference in the TNSS score and TNSS duration score between the experimental and placebo groups in weeks 1, 2, 3, or 4. For nasal congestion, fermented red ginseng was significantly effective (P<0.005), while placebo caused no change. The activity and emotion of RQoL improved markedly secondary to treatment with fermented red ginseng (P<0.05), while placebo caused no change. Additionally, fermented red ginseng reduced skin reactivity to sensitized perennial allergens (P<0.05). Fermented red ginseng was well tolerated. Fermented red ginseng improved nasal congestion symptoms and RQoL in patients with perennial allergic rhinitis.[12]

Estrogenic activity

The estrogenic effects of ginseng are controversial. Some clinical evidence suggests it doesn't have estrogen-mediated effects such as increasing follicle-stimulating hormone (FSH), estradiol levels, or endometrial thickness. However, case reports of ginseng side effects such as postmenopausal vaginal bleeding suggest estrogen activity. Panax ginseng extract has been shown to increase serum ceruloplasmin oxidase activity (a measure of estrogenic activity in the liver) in animal models when ovaries are removed. *In vitro* research also shows estrogen activity**.**[13-15]

Antiulcer activity

The effects of Korean red ginseng (KRGCD) on gastric ulcer models in mice. Stomach ulcers were induced by oral ingestion of hydrochloride (HCl)/ethanol or indomethacin. Treatment with KRGCD (30, 100, and 300 mg/kg, p.o.) occurred 1 hr before the ulcer induction. Effect of KRGCD on anti-oxidant activity and gastric mucosal blood flow with a laser Doppler flow meter in mice stomach tissue was evaluated. KRGCD (100 and 300 mg/kg, p.o.) significantly decreased ethanol and indomethacin-induced gastric ulcer compared with the vehicle-treated (control) group. KRGCD (100 and 300 mg/kg) also decreased the level of thiobarbituric acid reactive substance (TBARS) and increased gastric mucosal blood flow compared with the control group. These results suggest that the gastroprotective effects of KRGCD on mice ulcer models can be attributed to its ameliorating effect on oxidative damage and improving effect of gastric mucosal blood flow.[16]

Antidiabetic activity

The antiobesity effect and mechanism of action of Korean white ginseng extracts (KGE) using high-fat diet (HFD)-induced obese mice. Mice were fed a low-fat diet (LFD), HFD or HFD containing 0.8 and 1.6% (w/ w) KGE diet (HFD+0.8KGE and HFD+1.6KGE) for 8 weeks. We also examined the effects of KGE on plasma triglyceride (TG) elevation in mice administrated with oral lipid emulsion. Body weight gain and white adipose tissue (WAT) weight were significantly decreased in the HFD+1.6KGE group, compared with the HFD group. The plasma TG levels were also significantly reduced in both HFD 0.8KGE and HFD 1.6KGE groups, while leptin levels were significantly decreased in only the HFD1.6KGE group, compared with the HFD group. The HFD+1.6KGE group showed significantly lower mRNA levels of lipogenesis related genes, including peroxisome proliferator-activated receptorc 2 (PPARc2), sterol regulatory element binding protein-1c (SREBP-1c), lipoprotein lipase (LPL), fatty acid synthase (FAS) and diacylglycerol acyltransferase 1 (DGAT1), compared with the HFD group. In addition, a dose of 1000 mg/kg KGE inhibited the elevation of plasma TG levels compared with mice given the lipid emulsion alone. These results suggest that the anti-obesity effects of KGE may be elicited by regulating expression of lipogenesis-related genes in WAT and by delaying intestinal fat absorption.[17]

Antioxidant activity

Panax ginseng investigated the increase in free radical-scavenging activity of *Panax ginseng* as a result of heat-processing and its active compounds related to fortified antioxidant activity. In addition, the therapeutic potential of heat-processed ginseng (HPG) with respect to oxidative tissue damage was examined using rat models. Based upon chemical and biological activity tests, the free radical-scavenging active components such as less-polar ginsenosides and maltol in *Panax ginseng* significantly increased depending on the temperature of heat-processing. According to animal experiments related to oxidative tissue damage, HPG displayed hepatoprotective action by reducing the elevated thiobarbituric acid reactive substance (TBA-RS) level, as well as nuclear factor-kappa B (NF-κB) and inducible nitric oxide synthase (iNOS) protein expressions, while increasing heme oxygenase-1 in the lipopolysaccharide-treated rat liver and HPG also displayed renal protective action by ameliorating physiological abnormalities and reducing elevated TBA-RS, advanced glycation end product (AGE) levels, NF-κB, cyclooxygenase-2, iNOS, 3-nitrotyrosine, Nε-(carboxymethyl)lysine and receptors for AGE protein expression in the diabetic rat kidney. Therefore, HPG clearly has a therapeutic potential with respect to oxidative tissue damage by inhibiting protein expression related to oxidative stress and AGEs, and further investigations of active compounds are underway. This investigation of specified bioactive constituents is important for the development of scientific ginseng-derived drugs as part of ethnomedicine.[18]

The antioxidation effect of ginseng extract directly inhibits decomposition of unsaturated fatty acid caused by iron and hydrogen peroxide-induced lipidperoxidation and whether this effect involves a hydroxyl radical-scavenging mechanism. Thiobarbituric acid-reactive substances (TBARS), gas chromatography, and electron spin resonance (ESR) spectrometer were used to measure lipid peroxidation, unsaturated fatty acid, and hydroxyl radical. The results showed TBARS formed and the loss of arachidonic acid during lipid peroxidation, and that hydroxyl radical formed by the Fenton reaction were completely inhibited by ginseng extract. This antioxidant effect of ginseng may be responsible for its wide pharmacological actions in clinical practice by a free radical reaction-inhibition mechanism.[19]

Immune enhancement activity

Panax ginseng in this study to determine the immune-enhancement effect of *P. ginseng* using a forced swimming test (FST) and by measuring cytokine production in MOLT-4 cell culture and mouse peritoneal macrophages. *P. ginseng* was orally administered to mice once a day for 7 days. The anti-immobility effect of *P. ginseng* on the FST and blood biochemical parameters related to fatigue, glucose (Glc); blood urea nitrogen

(BUN); lactic dehydrogenase (LDH); total protein (TP) and production of cytokines in human T cell line, MOLT-4 cells and mouse peritoneal macrophages were investigated. After two and seven days, the immobility time was decreased in the *P. ginseng* administrated mice as compared to the control group; however, this reduction was not significant. In addition, the amount of TP in the blood serum was significantly increased. However, the levels of Glc, BUN and LDH did not show a significant change. *P. ginseng* significantly (P<0.05) increased interferon (IFN)-g production and expression as compared to control at 48 h in MOLT-4 cells. *P. ginseng* plus recombinant IFN-g instead of *P. ginseng* alone significantly increased the production of the tumour necrosis factor (TNF)-a in the mouse peritoneal macrophages.[20]

Anticancer activity

The intake of ginseng may reduce the risk of several types of cancer. When ginseng was tested in animal models, a reduction in cancer incidence and multiplicity at various sites was noted. Panax ginseng and its chemical constituents have been tested for their inhibiting effect on putative carcinogenesis mechanisms (e.g., cell proliferation and apoptosis, immunosurveillance, angiogenesis); in most experiments inhibitory effects were found. While Panax ginseng C. A. Meyer has shown cancer-preventive effects both in experimental models and in epidemiological studies, the evidence is currently not conclusive as to its cancer-preventive activity in humans. The available evidence warrants further research into the possible role of ginseng in the prevention of human cancer and carcinogenesis.[21]

Anti-hyperglycemic activity

Anti-hyperglycemic effect between *Panax ginseng* root and *Panax ginseng* berry in *ob/ob* mice, which exhibit profound obesity and hyperglycemia that phenotypically resemble human type-2 diabetes. Observation was that *ob/ob* mice had high baseline glucoselevels (195 mg/dl). Ginseng root extract (150 mg/kg body wt.) and ginseng berry extract (150 mg/kg body wt.) significantly decreased fasting blood glucose to 143 ± 9.3 mg/dl and 150 ± 9.5 mg/dl on day 5, respectively (both P < 0.01 compared with the vehicle). On day 12, although fasting blood glucose level did not continue to decrease in the root group (155 ± 12.7 mg/dl), the berry group became normoglycemic (129 ± 7.3 mg/dl;P< 0.01). Further glucose tolerance was evaluated using the intraperitoneal glucose tolerance test. On day 0, basal hyperglycemia was exacerbated by intraperitoneal glucose load, and failed to return to baseline after 120 min. After 12 days of treatment with ginseng root extract (150 mg/kg body wt.), the area under the curve (AUC) showed some decrease (9.6%). However, after 12 days of treatment with ginseng berry extract (150 mg/kg body wt.), overall glucose exposure improved significantly, and the AUC decreased 31.0% (P < 0.01). In addition, it was observed that body weight did not change significantly after ginseng root extract (150 mg/kg body wt.) treatment, but the same concentration of ginseng berry extract significantly decreased body weight (P < 0.01). These data suggest that, compared to ginseng root, ginseng berry exhibits more potent anti-hyperglycemic activity and only ginseng berry shows marked anti-obesity effects in *ob/ob* mice.[22]

The antihyperglycemic effects of the total ginsenosides in Chinese ginseng (TGCG), extracted from leaves and the stem, were evaluated in diabetic C57BL/6J *ob/ob* mice.

Animals received daily intraperitoneal injections of TGCG (100 and 200 mg/kg) or oral administration (150 and 300 mg/kg) for 12 days. Fasting blood glucose levels and body weight were measured after fasting the animals for 4 h. Peripheral glucose use was also measured using an intraperitoneal glucose tolerance test. In the injection group, a high dose of TGCG (200 mg/kg) significantly lowered the fasting blood glucose levels in *ob/ob* mice on day 12 (153 ± 16 mg/dL vs 203±9.8 mg/dL, P<0.01, compared to vehicle-treated group). In the oral group, blood glucose decreased notably with a dose of TGCG (300 mg/kg) on d 12 (169.1±12.6 mg/dL vs211.6±13.8 mg/dL, P<0.05, compared to the vehicle-treated group). Glucose tolerance was also improved markedly in *ob/ob* mice. Furthermore, a significant reduction in bodyweight (P<0.05) was observed after 12 days of TGCG (300 mg/kg) treatment in mice from the oral group. The results indicated that in a diabetic *ob/ob* mouse model TGCG was endowed with significant anti-hyperglycemic and anti-obesity properties. Therefore, the total ginsenosides extracted from Chinese ginseng leaves and the stem may have some potential for treating diabetes.[23]

Antidiabetic activity

Antiobese effects of *Panax ginseng* berry extract and its major constituent is ginsenoside Re, in obese diabetic C57BL/6J *ob*/*ob* mice and their lean littermates. Animals received daily intraperitoneal injections of *Panax ginseng* berry extract for 12 days. On day 12, 150 mg/kg extract treated *ob*/*ob* mice became normoglycemic (137±6.7 mg/dl) and had significantly improved glucose tolerance. The overall glucose excursion during the 2-h intraperitoneal glucose tolerance test decreased by 46% (P < 0.01) compared with vehicle treated *ob*/*ob* mice. The improvement in blood glucose levels in the extract-treated *ob*/*ob* mice was associated with a significant reduction in serum insulin levels in fed and fasting mice. A hyperinsulinemic-euglycemic clamp study revealed a more than twofold increase in the rate of insulin-stimulated glucose disposal in treated *ob*/*ob* mice (112±19.1 vs. 52±11.8 µmol $kg^{-1}min^{-1}$ for the vehicle group, P < 0.01). In addition, the extract-treated *ob*/*ob* mice lost a significant amount of weight (from 51.7±1.9 g on day 0 to 45.7±1.2 on day 12, P < 0.01 vs. vehicle treated *ob*/*ob* mice), associated with a significant reduction in food intake (P < 0.05) and a very significant increase in energy expenditure (P < 0.01) and body temperature (P < 0.01). Treatment with the extract also

significantly reduced plasma cholesterol levels in *ob*/*ob* mice. This antidiabetic effect of ginsenoside Re was not associated with body weight changes, suggesting that other constituents in the extract have distinct pharmacological mechanisms on energy metabolism.[24]

An aqueous methanol/water extract of the Oriental crude drug "ninjin" (ginseng), *Panax ginseng* roots showed a remarkable hypoglycaemic activity on administration to mice. Fractionation of the extract, along with the pharmacological assays, led to isolation of five glycans, panaxans A, B, C, D and E. These constituents exhibited significant hypoglycaemic actions in normal and alloxan-induced hyperglycaemic mice.[25]

Anti muscle injury

Eccentric muscle contraction causes fibre injury associated with disruption of the myofibrillar cytoskeleton. The medicinal plant *Panax ginseng* C.A. Meyer, known for its therapeutic properties, was studied to explore its protective effects after eccentric contraction. A crude extract and a standardised extract (G115) of different Saponin compositions were tested as to their efficacy in reducing lipid peroxidation, inflammation and release of myocellular proteins after the realisation of an eccentric contraction protocol on a rat treadmill. Plasma creatine kinase (CK) levels were significantly reduced by approximately 25% after ingestion of both extracts of ginseng. Both extracts reduced lipid peroxidation by approximately 15% as measured by malondialdehyde levels. β-Glucuronidase concentrations and glucose-6-phosphate dehydrogenase (G6PD H) levels, which can be considered markers of inflammation, were also significantly reduced. The values of β-glucuronidase were increased from 35.9±1.5 to 128.4±8.1 in vastus and to 131.1±12.1 U g^{-1} in rectus, the protection due to ginseng administration being approximately 40% in both muscles. Both extracts appeared to be equally effective in reducing injuries and inflammation caused by eccentric muscle contractions.[26]

Anxiolytic activity

The putative anxiolytic activity of the white and red varieties of ginseng, the root of *Panax ginseng*, was investigated in rats and mice using a number of experimental paradigms of anxiety and compared with that of diazepam. Pilot studies indicated that single-dose administration of ginseng had little to no acute behavioural effects, hence the two varieties of ginseng were administered orally at two dose levels twice daily for 5 days, while diazepam (1 mg/kg, i.p.) was administered acutely. White and red varieties of ginseng (20 and 50 mg/kg) showed positive results when tested against several paradigms of experimental anxiety. Both were effective in the open-field and elevated plus-maze tests and reduced conflict behaviour in thirsty rats and footshock-induced fighting in paired mice. Ginseng also attenuated pentylenetetrazole-induced decrease in rat brain MAO activity, confirming its anxiolytic activity since this has been proposed to be an endogenous marker for anxiety. The effects induced by white and red ginseng (50 mg/kg × 5 days) were comparable to those induced by diazepam (1 mg/kg).[27]

Analgesic activity

The effect of intraperitoneal administration of *Panax ginseng* on the development of tolerance to the analgesic and hyperthermic actions of morphine was determined in male Sprague-Dawley rats. Rats were rendered tolerant to morphine to different degrees by the subcutaneous implantation of either four pellets of morphine over a 3-day period or six pellets over a 7-day period. Each pellet contained 75 mg of morphine free base. Rats serving as controls were implanted with placebo pellets. Daily administration of ginseng extract (6.25–50.0 mg/kg) for 3 days inhibited the development of tolerance to the analgesic effect but not to the hyperthermic effect of morphine in the four pellet schedule. In six pellet schedule, daily administration of ginseng extract (25 and 50 mg/kg) for 7 days also inhibited the development of tolerance to the analgesic effect of morphine, but the 100 mg/kg dose had no effect. On the other hand, in six pellet schedule, the administration of ginseng extract (50 and 100 mg/kg) once daily for 7 days inhibited the development of tolerance to the hyperthermic effect of morphine. It is concluded that in appropriate doses, ginseng extract has inhibitory activity on the development of tolerance to the pharmacological actions of morphine.[28]

Cardiovascular activity

Ether, ethanol and aqueous extracts of ginseng were serially prepared from Korean ginseng plants. Each extract in the dose of 40 mg/kg was administered intravenously to ten dogs under light halothane anesthesia while 11 cardiovascular variables were compared during the ensuing two hours. The variables included cardiac output, stroke volume, heart rate, mean arterial pressure, pulse pressure, central venous pressure, total peripheral resistance, pH, $PaCO_2$, PaO_2 and base deficit. Following the administration of the ether extract (40 mg/kg) the heart rate and the central venous pressure decreased significantly. The administration of ethanol extract (40 mg/kg) caused a significant decrease in the heart rate and the mean arterial pressure. After the administration of the aqueous extract (40 mg/kg) the cardiac output, stroke volume and central venous pressure were significantly decreased, while the total peripheral resistance was significantly increased.[29]

Calcium channel inhibition

A crude extract from ginseng root inhibits high-threshold, voltage-dependent Ca^{2+} channels through an unknown receptor linked to a pertussis toxin-sensitive G protein. We now have found the particular compound that seems responsible for the effect: it is a saponin, called ginsenoside Rf (RI), that is present in only trace amounts within ginseng. At saturating concentrations, Rf rapidly and reversibly inhibits N-type, and other high threshold,

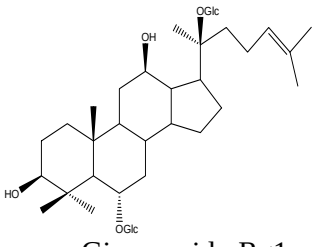
Ca^{2+} channels in rat sensory neurons to the same degree as a maximal dose of opioids. The effect is dose-dependent (half-maximal inhibition: 40 uM) and it is virtually eliminated by pretreatment of the neurons with pertussis toxin, an inhibitor of Go and G1 GTP-binding proteins. Other ginseng saponins-ginsenosides Rbl, Rc, Re, and Rgl caused relative little inhibition of Ca^{2+} channels and lipophilic components of ginseng root had no effect. Antagonists of a variety of neurotransmitter receptors that inhibit Ca^{2+} channels fail to alter the effect of Rf, raising the possibility that Rf acts through another G protein-linked receptor. Rf also inhibits Ca^{2+} channels in the hybrid F-li cell line, which might, therefore, be useful for molecular characterization of the putative receptor for Rf. Because it is not a peptide and it shares important cellular and molecular targets with opioids, Rf might be useful in itself or as a template for designing additional modulators of neuronal Ca^{2+} channels.[30]

PHYTOCHEMICALS

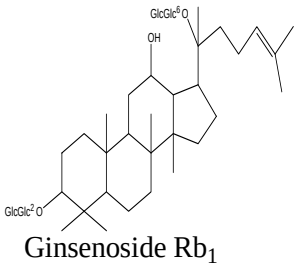
Panax ginseng contains several active constituents. The root of the ginseng plant is constituted of organic (80%–90%) and inorganic substances (approximately 10%) and consists of a number of active constituents, such as saponins or ginsenosides, carbohydrates (including polysaccharides), nitrogenous substances, amino acids, peptides, phytosterol, essential oils, organic acids, vitamins, and minerals.[31] Ginsenosides triterpenoids are the principal bioactive constituents of ginseng that have also been used as marker compounds for the Panax species.[32,33] Most commonly studied ginsenosides are Rb1, Rg1, Rg3, Re, Rd and Rh1.[33] Other constituents include pectin, B vitamins, and various flavonoids Panax ginseng also contains the peptidoglycans, panaxans.[34] The genuine sapogenins of those saponins, 20(S)-protopanaxa-diol and -triol, were identified as 20(S) 12–hydroxy and 20(S) 6, 12 -dihydroxy-dammarenediol-II, respectively. Some partly deglycosylated saponins such as ginsenoside Rh-1, Rh-2, and Rg-3 are obtained from red ginseng as artifacts produced during steaming. [35]

GINSENOSIDES AND ITS PHARMACOLOGICAL ACTIVITIES

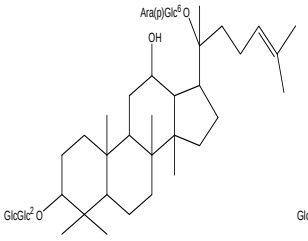
The major biologically active compounds in ginseng are ginsenosides and their activities are cardiovascular diseases, cancer, immune deficiency, and hepatotoxicity. Moreover, recent research has suggested that some of ginseng's active ingredients also exert beneficial effects on aging, central nervous system (CNS) disorders, and neurodegenerative diseases. In general, antioxidant, anti-inflammatory, anti-apoptotic, and immune-stimulatory activities are mostly underlying the possible ginseng-mediated protective mechanisms. Next to animal studies, data from neural cell cultures contribute to the understanding of these mechanisms that involve decreasing nitric oxide (NO), scavenging of free radicals and counteracting excitotoxicity.[36-47] Ginsenosides and polysaccharides are not easily absorbed by the body through the intestines due to their hydrophilicity. Therefore, these constituents which include ginsenosides Rb1, Rb2, and RC, inevitably come into contact with intestinal microflora in the alimentary tract and can be metabolized by intestinal microflora. Since most of the metabolites such as compound K and protopanaxatriol are nonpolar compared to the parental components, these metabolites are easily absorbed from the gastrointestinal tract. The absorbed metabolites may express pharmacological actions, such as antitumor, antidiabetic, anti-inflammatory, anti-allergic, and neuroprotective effects.[48] Ginsenoside Rg1, raises blood pressure and acts as a central nervous system (CNS) stimulant. Ginsenoside Rb1 lowers blood pressure and acts as a CNS depressant. They also seem to interfere with platelet aggregation and coagulation. Ginsenosides also potentiate nerve growth factor and might confer neuroprotection through nicotinic activity. There is also evidence that ginsenosides can relax human bronchial smooth muscle by stimulating the release of nitrous oxide from airway epithelium which may account for the potential anti-asthmatic effect of Panax ginseng. However, research on related ginseng species, Panax pseudoginseng, suggests these ginsenosides may not be pharmacologically significant. Rb1 has a low oral bioavailability, and Rg1 is rapidly eliminated from the blood in animal models. Panax ginseng may lower serum cholesterol and triglycerides, possibly by increasing lipoprotein lipase activity, which enhances lipid metabolism. Panax ginseng and other ginsengs contain protopanaxadiol (PPD) ginsenosides, Rb1, Rb2, Rc, and Rd. They also contain protopanaxatriol (PPT) ginsenosides, Rg1, Re, and Rf. A higher ratio of PPD ginsenosides to PPT ginsenosides is related to greater blood glucose and insulin lowering potency of the ginseng product. Specifically its constituent ginsonside-Rb1, acts as a phytoestrogen. Panaxagin, a protein isolated from unprocessed ginseng root, seems to have antiviral and antifungal activity, according to preliminary research. It appears to inhibit HIV reverse transcriptase and ribosomal activity of some fungi.[34, 49-62]



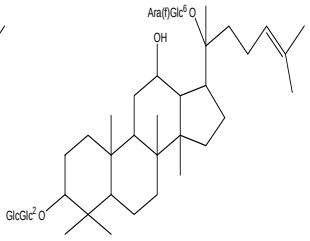
Ginsenoside-Rg1



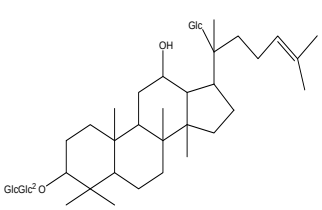
Ginsenoside Rb_1



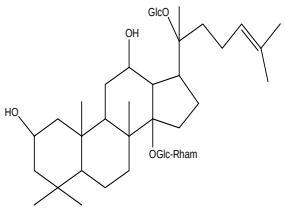
Ginsenoside Rb_2



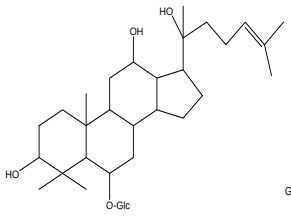
Ginsenoside Rc



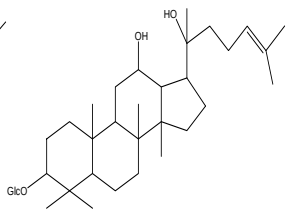
Ginsenoside Rd



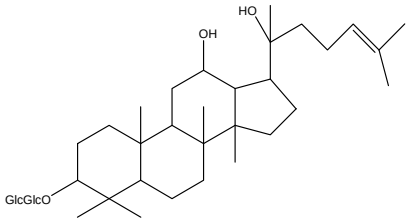
Ginsenoside Re



Ginsenoside Rh_1



Ginsenoside Rh_2



Ginsenoside Rp1

Hepatoprotective activity

Despite regular exercise benefits, acute exhaustive exercise elicits oxidative damage in liver. The present study determined the hepatoprotective properties of ginsenoside-Rg1 against exhaustive exercise-induced oxidative stress in rats. Forty rats were assigned into vehicle and ginsenoside-Rg1 groups (0.1 mg/kg bodyweight). After 10-week treatment, ten rats from each group performed exhaustive swimming. Estimated oxidative damage markers, including thiobarbituric acid reactive substance (TBARS) (67%) and protein carbonyls (56%), were significantly ($P < 0.01$) elevated after exhaustive exercise but alleviated in ginsenoside-Rg1 pretreated rats. Furthermore, exhaustive exercise drastically decreased glutathione (GSH) content (~79%) with concurrent decreased superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities. However, these changes were attenuated in Rg1 group. Additionally, increased xanthine oxidase (XO) activity and nitric oxide (NO) levels after exercise.[63] were also inhibited by Rg1 pretreatment. For the first time, our findings provide strong evidence that ginsenoside-Rg1 can protect the liver against exhaustive exercise-induced oxidative damage. Ginsenoside is a active triterpenoid obtained from *Panax ginseng* use in treatment of chronic diseases Obesity, Diabetes, Cardiovascular, Arthritis inflammation.[64]

Intestinal ischemia-reperfusion (I/R) is an important event in the pathogenesis of multiple organ dysfunction syndrome (MODS). This study is to determine the effects of ginsenoside Rb1 on liver injury induced by intestinal I/R in rats. Adult male Wistar rats were randomly divided into four groups: (1) a control, sham-operated group (sham group); (2) an intestinal I/R group subjected to 1 h intestinal ischemia and 2 h reperfusion (I/R group); (3) a group treated with 20 mg/kg ginsenoside Rb1 before reperfusion (Rb1-20 group); and (4) a group treated with 40 mg/kg ginsenoside Rb1 before reperfusion (Rb1-40 group). Liver and intestinal histology was observed. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) level in serum and malondialdehyde (MDA) level in intestinal tissues were measured. Myeloperoxidase (MPO), TNF-α, MDA level and immunohistochemical expression of NF-κB and intracellular adhesion molecule- 1 (ICAM-1) in liver tissues was assayed. In addition, a western blot analysis of liver NF-κB expression was performed. Results indicated intestinal I/R induced intestinal and liver injury, which was characterized by increase of AST and ALT in serum, MDA level in intestine, MPO, TNF-α and MDA level and ICAM-1 and NF-κB expression in the liver tissues. Ginsenoside Rb1 (20, 40 mg/kg) ameliorated liver injury, decreased MPO, TNF-α and MDA level, NF-κB and ICAM-1 expression in liver tissues. In conclusion, ginsenoside Rb1 ablated liver injury induced by intestinal I/R by inhibiting NF-κB activation.[65]

Diuretic activity

To determine if soy extract or Panax ginseng increases the urinary excretion of the 6-ß-hydroxycortisol/cortisol ratio as a marker of cytochrome P450 (CYP) 3A enzyme induction, subjects received a soy extract containing 50 mg isoflavones twice daily (n = 20) or Panax ginseng 100 mg standardized to 4% ginsenosides twice daily (n = 20) for 14 days. Neither Panax ginseng nor soy extract significantly altered the urinary 6-ß-OH-cortisol/cortisol ratio, suggesting that unlike St. John's wort, they are not CYP3A inducers. Studies in vitro using human liver microsomes were performed to determine the effect of soy extract on probe substrates of CYP and UDP glucuronosyltransferase (UGT). Unhydrolyzed soy extract produced very little inhibition of CYP1A2, CYP2A6, and CYP2D6 and a trend of activation of CYP3A4. Hydrolyzed soy extract showed inhibition of all of the CYPs tested, particularly CYP2C9 and CYP3A4. UGT2B15 was the only UGT significantly inhibited. Even though both soy extract and ginseng have been shown to activate CYP3A4 in vitro, there is a lack of an in vitro correlation with the in vivo effects.[66]

Poor accessibility to the brain

Ginsenosides, are characterized by poor accessibility to the brain, and this pharmacokinetic-pharmacological paradox remains poorly explained are also effective in treating lipopolysaccharide- (LPS) induced depression-like behavior and neuroinflammation. In an LPS-induced depression-like behavior model, the antidepressant effects of ginseng total saponins (GTS) were assessed using a forced swimming test, a tail suspension test, and a sucrose preference test. The anti-inflammatory efficacies of GTS in brain, plasma, and LPS-challenged RAW264.7 cells were validated using ELISA and quantitative real-time PCR. Moreover, indoleamine 2,3-dioxygenase (IDO)

activity in the periphery and brain were also determined by measuring levels of kynurenine/tryptophan. GTS significantly attenuated LPS-induced depression-like behavior. Moreover, LPS-induced increases in 5-HT and tryptophane turnover in the brain were significantly reduced by GTS. IDO activities in brain and periphery were also suppressed after pretreatment with GTS. Furthermore, GTS-associated recovery from LPS-induced depression-like behavior was paralleled with reduced mRNA levels for IL-1β, IL-6, TNF-αs, and IDO in hippocampus. Poor brain distribution of ginsenosides was confirmed in LPS-challenged mice. GTS treatment significantly decreased production of various proinflammatory cytokines in both LPS-challenged mice and RAW264.7 cells. This study suggests that the anti-depression efficacy of GTS may be largely attributable to its peripheral anti-inflammatory activity.[67]

Antifatigue activity

Despite uncertainty about its mechanism of action, a limited number of placebo-controlled trials have suggested that ginseng is capable of decreasing fatigue. Of particular interest, one placebo-controlled trial of 501 healthy adults with complaints of stress and fatigue demonstrated an overall improved quality of life after a 12-week treatment trial with an Asian ginseng extract.[68] Another large placebo-controlled trial of ginseng in 384 postmenopausal women with complaints of stress and fatigue demonstrated improved general wellbeing after 16 weeks of treatment.[69] Because ginseng appeared to be useful for fatigue in other populations, Kim *et al.* conducted a double-blind placebo-controlled crossover pilot trial of American ginseng extract using an escalating daily dose of 100 mg, 200 mg and 400 mg for the first 3 weeks of a 6-week intervention period in subjects with MS to determine its effects on fatigue.[70] However, this study failed to show any benefit of American ginseng extract on fatigue in these subjects with MS. Some subjects experienced insomnia while on American ginseng, suggesting that higher doses might not be tolerated. Thus American ginseng does not appear to be a promising treatment for fatigue in MS. Ginseng extracts appear to be safe, although large doses can cause side effects. Ginseng extracts have been used at doses of up to 2 g per day without adverse effects.[71,72] Excessive intake of ginseng (with dosing at 3–15 g per day) has been associated with hypertension, nervousness, irritability, insomnia, rash and diarrhea.[73] Five different animal models using conventional toxicological methods reported no acute or chronic toxicity of the extract.[74,75]

Antihuntington activity

Nanomolar concentrations of ginsenoside Rb1 and Rc effectively protected YAC128 medium spiny neurons from glutamate-induced apoptosis and that Rg5 was protective at micromolar concentration. The other seven ginsenosides tested were not effective or exerted toxic effects in MSN cultures. From these results we concluded that ginsenosides Rb1, Rc and Rg5 offer a potential therapeutic choice for the treatment of HD and possibly other neurodegenerative disorders.[76]

Anticancer activity

Angiogenesis is a crucial step in tumour growth and metastasis. Ginsenoside-Rb1 (Rb1), the major active constituent of ginseng, potently inhibits angiogenesis in vivo and in vitro. However, the underlying mechanism remains unknown. The potent anti-angiogenic protein, pigment epithelium-derived factor (PEDF), is involved in regulating the anti-angiogenic effects of Rb1. Rb1-induced PEDF was determined by real-time PCR and western blot analysis. The antiangiogenic effects of Rb1 were demonstrated using endothelial cell tube formation assay. Competitive ligand-binding and reporter gene assays were employed to indicate the interaction between Rb1 and the oestrogen receptor (ER). Rb1 significantly increased the transcription, protein expression and secretion of PEDF. Targeted inhibition of PEDF completely prevented Rb1-induced inhibition of endothelial tube formation, suggesting that the anti-angiogenic effect of Rb1 was PEDF specific. Interestingly, the activation of PEDF occurred via a genomic pathway of ERb. Competitive ligand binding assays indicated that Rb1 is a specific agonist of ERb, but not ERa. Rb1 effectively recruited transcriptional activators and activated an oestrogen-responsive reporter gene. Furthermore, Rb1-mediated PEDF activation and the subsequent inhibition of tube formation were blocked by the ER antagonist ICI 182,780 or transfection of ERb siRNA, indicating ERb dependence. Rb1 suppressed the formation of endothelial tube-like structures through modulation of PEDF via ERb.[77]

Ginsenosides have been shown to inhibit tumor cell invasion and suppress sister chromatid exchanges in human lymphocytes. Panax ginseng also contains water insoluble polyacetylenic constituents such as panaxynol, panaxydol and panaxytriol. Panaxydol seems to have antiproliferative effects on various types of cancer cells by inhibiting cancer cell growth at the cell cycle G1 to S transition phase. In peptic ulceration, Panax ginseng has shown inhibitory activity on Helicobacter pylori-induced hemagglutination. Samgyetang, a soup made from chicken, panax ginseng, garlic, jujube, and chestnuts, appears to offer protection from experimentally induced peptic ulcers.[13-15]

Ginsenosides, can be classified as protopanaxadiol and protopanaxatriol groups. In addition, various steaming temperature and time treatment of the ginseng herbs can change ginsenoside profiles, and enhance their anti-cancer activities. This heat treatment process may increase the role of ginseng in treating colorectal cancer.[78]

Ginsenosides, is the dammarane-type triterpene saponin constituents of *Panax* species. Several ginsenosides, namely Rg1, Rg3, Re, Rc and Rd inhibited drug efflux.[79] A combination of purified saponins containing Rb1, Rb2, Rc, Rd, Re and Rg1 reversed MDR whereas individual

ginsenosides did not produce any effect.[80] Ginsenosides reversed MDR of several chemotherapeutic drugs such as homoharringtonine, cytarabine, doxorubicin and etoposide in K562/VCR and in a dose-dependent manner in K562/DOX. Pgp expression decreased but bcl-2 expression remained the same. Rb1 reversed MDR of harringtonolide and vincristine in K562/HHT and HL60/VCR cell lines respectively.[81-83]

The normally analyzed neutral ginsenosides vary in level and ratio among the different *Panax* species, and they are accompanied in unprocessed root by acid derivatives of malonic acid. These derivatives are readily hydrolyzed by the steaming process, which converts "white" ginseng to "red" ginseng (actually caramel-colored). The steaming process also converts original ginsenosides to partially deglycosylated derivatives that have enhanced anti-cancer activity (e.g., ginsenosides Rg3, Rg5, and Rh2).[84]

Compound K [20-*O*-β-(D-glucopyranosyl)-20(S)-protopanaxadiol], a metabolite of the protopanaxadiol-type saponins of *Panax ginseng* C.A. Meyer, has been reported to possess antitumor properties to inhibit angiogenesis and to induce tumor apoptosis. In the present study, we investigated the effect of Compound K on apoptosis and explored the underlying mechanisms involved in HL-60 human leukemia cells. The effect of Compound K on the viabilities of various cancer cell lines studied by MTT assays. DAPI assay, Annexin V and PI double staining, Western blot assay and Immuno precipitation were used to determine the effect of Compound K on the induction of apoptosis. Compound K was found to inhibit the viability of HL-60 cells in a dose and time dependent manner with an IC50 of 14 μM. Moreover, this cell death had typical features of apoptosis, that is, DNA fragmentation, DNA ladder formation, and the externalization of Annexin V targeted phosphatidylserine residues in HL-60 cells. In addition, compound-K induced a series of intracellular events associated with both the mitochondrial- and death receptor-dependent apoptotic pathways, namely, the activation of caspases-3, -8, and -9; the loss of mitochondrial membrane potential; the release of cytochrome *c* and Smac/DIABLO to the cytosol; the translocation of Bid and Bax to mitochondria; and the down regulations of Bcl-2 and Bcl-xL. Furthermore, a caspase-8 inhibitor completely abolished caspase-3 activation, Bid cleavage, and subsequent DNA fragmentation by Compound K. Interestingly, the activation of caspase-3 and -8 and DNA fragmentation were significantly prevented in the presence of cycloheximide, suggesting that Compound K-induced apoptosis is dependent on *de novo* protein synthesis. The results indicate that caspase-8 plays a key role in Compound K-stimulated apoptosis via the activation of caspase-3 directly or indirectly through Bid cleavage, cytochrome *c* release, and caspase-9 activation.[85]

The saponin constituents and anticancer activities of steamed American ginseng (*Panax quinquefolius* L.) roots were evaluated. The contents of 12 ginsenosides in the roots were determined using high performance liquid chromatography (HPLC). After the steaming treatment (100 – 120° C for 1 h and 120°C for 0.5 – 4 h), the quantity of 7 ginsenosides decreased and that of 5 others increased. The content of ginsenoside Rg3, a previously recognized anticancer compound, increased significantly when the root was steamed at 120 °C for 0.5 – 3 h. The antiproliferative effects of unsteamed and steamed (120°C for 1 h and 2 h) American ginseng root extracts were assayed by the modified trichrome stain (MTS) method using three cancer cell lines (SW-480, HT-29, NSCLC). Heat-processing increased the antiproliferative effect of American ginseng significantly, and the activity of the extract from roots steamed for 2 h was greater than that of roots steamed for 1 h. Chemical constituents and antiproliferative activities of white and red Asian ginseng have also been evaluated. Five representative ginsenosides, Rb1, Rd, Re, Rg2 and Rg3, were studied. Ginsenoside Rg3 had the most potent effect. The antiproliferative activities of red American ginseng are augmented when ginsenoside Rg3 is increased.[86]

Investigating the molecular mechanisms involved in mediating its actions in human breast cancer (MCF-7) cells. Rg1 (1 pM) stimulates cell proliferation ($P<0.01$) and estrogen-responsive pS2 mRNA expression ($P<0.05$) without alteration of estrogen receptor alpha (ERά) protein or mRNA expression in MCF-7 cells. In addition, 10^{-14}–10^{-4}M of Rg1 does not demonstrate specific binding to ERά. We hypothesize that Rg1 may exert its actions in MCF-7 cell via the activation of crosstalk between ER- and insulin growth factor I receptor (IGF-IR)-dependent pathways. The results indicate that Rg1 significantly increases IGF-IR expression and IGF-IR promoter activity in MCF-7 cells ($P<0.05$). Co-treatment of MCF-7 cells with 1 μM of estrogen antagonist ICI 182,780 completely abolishes the effects of Rg1 on IGF-IR expression. Furthermore, Rg1 enhances tyrosine phosphorylation of IRS-1 in MCF-7 cells upon IGF-I stimulation and the activation of IRS-1 phosphorylation is also ER-dependent. Taken together, our results suggest that Rg1 not only increases IGF-IR expression but also enhances IGF-IR-mediated signaling pathways in MCF-7 cells. The stimulation of IGF-IR expression by Rg1 in MCF-7 cells appears to require ER, and its actions might involve ligand-independent activation of ER.[87]

Antineurodegenrative activity

The active ingredient of *Panax* ginseng, with cocaine attenuate cocaine induced enhancement of evoked DA (dopamine) release, DA uptake inhibition and/or withdrawal-associated rebound enhancement. Cocaine rapidly potentiated the DA release within the first 10 min of application and acute cocaine withdrawal caused a rebound increase. Co-application of GTS with cocaine inhibited the release enhancement and subsequently prevented the rebound increase during acute withdrawal. The effect of GTS was concentration-dependent. In

contrast, GTS had no significant effects on the cocaine-mediated DA uptake inhibition. These results suggest that the attenuation of the cocaine-induced enhancement of impulse-dependent DA release, rather than uptake inhibition, might be one of the pharmacological bases for attenuation of behavioral effects of cocaine and amelioration of acute withdrawal symptoms by ginseng.[88]

Antihippocampal activity

Ginseng total saponins (GTSs) protect hippocampal neurons after experimental traumatic brain injury (TBI) in rats. A moderate-grade TBI was made with the aid of a controlled cortical impact (CCI) device set at a velocity of 3.0 m/sec, a deformation of 3.0 mm and a compression time of 0.2 sec at the right parietal area for adult male Sprague-Dawley rats. Shamoperated rats that underwent craniectomy without impact served as controls. GTSs (100 and 200 mg/kg) or saline was injected intraperitoneally into the rats immediately post-injury. Twenty-four hours after the injury, the rats underwent neurological evaluation. Contusion volume and the number of hippocampal neurons were calculated with apoptosis evaluated by TUNEL staining. 24 hr post-injury, saline injected rats showed a significant loss of neuronal cells in the CA2 region of the right hippocampus (53.4%, $p<0.05$) and CA3 (34.6%, $p<0.05$) compared with contralateral hippocampal region, a significant increase in contusion volume (34±8 L), and significant increase in neurologic deficits compared with the GTSs groups. Treating rats with GTSs seemed to protect the CCI-induced neuronal loss in the hippocampal , decrease cortical contusion volume, and improve neurological deficits.[89]

Antioxidant activity

The effects of ginsan, a polysaccharide fraction extracted from Panax ginseng, on the γ- radiation induced alterations of some antioxidant systems in the spleen of Balb/c mice. On the 5th day after sublethal whole-body irradiation, homogenized spleen tissues of the irradiated mice expressed only marginally increased mRNA levels of Mn-SOD (superoxide dimutase) in contrast to Cu/Zn-SOD, however, catalase mRNA was decreased by ~50% of the control. In vivo treatment of non-irradiated mice with ginsan (100 mg kg^{-1}, intraperitoneal administration) had no significant effect, except for glutathione peroxidase (GPx) mRNA, which increased to 144% from the control. However, the combination of irradiation with ginsan effectively increased the SODs and GPx transcription as well as their protein expressions and enzyme activities.

In addition, the expression of heme oxygenase-1 and non-protein thiol induced by irradiation was normalized by the treatment of ginsan. Evidence indicated that transforming growth factor-β and other important cytokines such as IL-1, TNF and IFN-γ might be involved in evoking the antioxidant enzymes. Therefore, we propose that the modulation of antioxidant enzymes by ginsan was partly responsible for protecting the animal from radiation, and could be applied as a therapeutic remedy for various ROS-related diseases.[90]

Calcium channel inhibition

The effect of the active ingredients of Panax ginseng, ginsenosides, on store operated Ca^{2+} entry (SOCE) using a two-electrode voltage clamp technique in Xenopus oocytes in which SOCE is monitored through Ca^{2+}activated Cl^- currents. Under hyperpolarizing voltage clamp conditions, treatment with ginsenosides produced a biphasic Ca^{2+} activated Cl^- current consisting of a rapid transient inward current and a slowly developing secondary sustained inward current. The transient inward current was inactivated rapidly, whereas the sustained inward current persisted for nearly 10 min. The effect of ginsenosides on the biphasic current was dose-dependent and reversible. The EC50 was 42.8±11.6 and 46.6±7.1μg$ml^{-1}$for the transient and sustained inward current, respectively. In the absence of extracellular Ca^{2+} ginsenosides induced only a transient inward current but in the presence of extracellular Ca^{2+}ginsenosides induced the biphasic current. Magnitudes of the sustained currents were dependent on extracellular Ca^{2+} concentration. Sustained inward current induced by ginsenosides, but not transient inward current, and ginsenoside-induced store-operated Ca^{2+} (SOC) currents (I_{SOC}) were blocked by La^{3+} a Ca^{2+} channel blocker, suggesting that the sustained inward current and ISOC was derived from an influx of extracellular Ca^{2+}.Treatment with 2-APB and heparin, which are IP_3 receptor antagonists, inhibited the ginsenoside induced biphasic current. Treatment with the PLC inhibitor, U73122, also inhibited the ginsenoside induced biphasic current. Intraoocyte injection of ATP-γS, but not adenylyl AMP-PCP, induced a persistent activation of ginsenoside-induced sustained current but did not affect the transient current. In rat hippocampal neurons, ginsenosides inhibited both carbachol-stimulated intracellular Ca^{2+} release and intracellular Ca^{2+} depletion-activated SOCE. These results indicate that ginsenoside might act as a differential regulator of intracellular Ca^{2+} levels in neurons and Xenopus oocytes.[91]

Cytoprotective effect

Ginsenoside Rg3 (Rg3) isolated from Panax ginseng relaxes vessels and exerts a cytoprotective effect. In view of the fact that nitric oxide (NO) is involved in vascular hyporeactivity and immunostimulation, the effects of total ginsenosides (GS) and Rg3 on the vascular responses and the expression of inducible nitric oxide synthase (iNOS) were investigated. Vasocontraction of endothelium-denuded aortic ring was induced by phenylephrine with or without GS or Rg3. The expression of iNOS was assessed by Western blot and RT–PCR analyses. NF-kB activation was monitored by gel shift, immunoblot and immunocytochemical analyses. Incubation of the endothelium-denuded aortic ring with GS or Rg3 inhibited phenylephrine induced vasocontraction, which was abrogated by NOS inhibition. GS or Rg3 increased NO production in aortic rings, but Rb1, Rc, Re and Rg1 had no effect. Aortic rings obtained

from rats treated with GS or Rg3 responded to phenylnephrine to a lesser extent, while producing NO to a larger extent, than those from control animals. GS or Rg3 induced iNOS in vascular smooth muscle. Rg3 induced iNOS with increase in NO production in Raw264.7 cells. Rg3 increased NF-kB DNA binding, whose band was super shifted with anti-p65and anti-p50 antibodies and elicited p65 nuclear translocation, which was accompanied by phosphorylation and degradation of I-kBa. PKC regulated iNOS induction by Rg3.[6] In conclusion, Rg3 relaxes vessels as a consequence of NO production, to which iNOS induction contributes, and iNOS induction by Rg3 accompanied NF-kB activation, which involves phosphorylation and degradation of I-kBa and nuclear translocation of p65.[92]

Anti-septicaemic activity

Anti-septicaemic effect of a polysaccharide (PS) isolated from *Panax ginseng* C.A. Meyer (Araliaceae) by nitric oxide production from stimulated macrophage. In vitro assays for the activity measurement of PS, NO production test with Greiss reagent, phagocytic activity test using zymosan and cytokines production test using ELISA kit were also conducted. In vivo anti-septicaemic activity was assessed by using C57BL/6J mice. This was done with *Staphylococcus aureus* infection test. PS used at 0.025 mg/kg concentration showed a potent anti-septicaemic activity (80%, survival). However, it did not directly inhibit *S. aureus* in a minimum inhibitory concentration (MIC) test, conducted in vitro (data not shown). Nitric oxide production via macrophage activation showed the highest value of 5.5 nmol/ml at 1 µg/ml PS. In *in-vitro* phagocytic activity test, PS at 10 µg/ml concentration showed a potent phagocytic activity for zymosan with 167% of the control. Production of TNF-α by macrophage activation at 10 µg/ml of PS was 96% lysis of L929. Also production of IL-1 and IL-6 by stimulation of macrophage with 100 µg/ml PS dose increased to 235 pg/ml and 0.47 ng/ml, respectively. The low mortality of PS treated (0.025 mg/kg) infected mice was concurrent with decreased bacterial content in the blood. Nitric oxide production in *S. aureus* infected mice whose macrophage was stimulated by PS (0.025 mg/kg) increased approximately 4 times than the untreated *S. aureus* infected group at 24 and 48 h incubation. In the PS treated (0.025 mg/kg) group, the intracellular concentration of *S. aureus* in macrophages decreased approximately by 50%, compared with the untreated group. Combine treatment with PS (0.025 mg/kg body weight) and vancomycin (10 mg/kg B.W.) resulted in 100% survival of the animals, whereas only 67% or 50% of the animals survived, respectively, when treated with PS or vancomycin alone. These results suggest that PS from *Panax ginseng* possess a potent anti-septicaemic activity by stimulating macrophage and a potentiality as an immunomodulator against sepsis occurred by *Staphylococcus aureus*.[93]

Cardiovascular activity

Ginsenoside, regulates cardiovascular function. This study was to examine the effect of ginsenosides Rb1 and Re on cardiac contractile function at the cellular level. Ventricular myocytes were isolated from adult rat hearts and were stimulated to contract at 0.5 Hz. Contractile properties analysed included: peak shortening (PS), time-to-90%PS (TPS), time-to-90% relengthening (TR_{90}), and fluorescence intensity change (ΔFFI). Nitric oxide synthase (NOS) activity was determined by the ^{3}H-arginine to ^{3}H-citrulline conversion assay. Both Rb1 and Re exhibited dose-dependent (1 ± 1000 nM) inhibition in PS and DFFI, with maximal inhibitions between 20 ± 25%. Concurrent application Rb1 and Re did not produce any additive inhibition on peak shortening amplitude (with a maximal inhibition of 24.9+6.1%), compared to Rb1 or Re alone. Pretreatment with the NOS inhibitor No-nitro-L-arginine methyl ester (L-NAME, 100 µM) abolished the effect of Rb1 and Re. Both Rb1 and Re significantly ($P<0.05$) stimulated NOS activity concentration-dependently. This study demonstrated a direct depressant action of ginsenosides on cardiomyocyte contraction, which may be mediated in part through increased NO production.[94]

Anti-inflammatory activity

Ginsenoside Ro, an oleanane-type saponin has been screened for activity in experimental models of inflammation. Ginsenoside Ro (10, 50, and 200 mg/kg, *p. o.*) inhibited an increase in vascular permeability in mice induced by acetic acid and reduced an acute paw edema in rats induced by compound 48/80 or carrageenin. Ginsenoside Ro did not suppress a developing adjuvant-induced edema in arthritic rats. However, ginsenoside Ro was found to be effective in hypercoagulable state, increase of connective tissue in the artery and calcium effluence from the bone in adjuvant-induced arthritic rats.[95]

Recent issues have arisen regarding ginsenosides's immunosuppressive and anti-inflammatory roles in inflammatory cells. This is because inflammation, managed by a large amount of different pro-inflammatory mediators such as cytokines, nitric oxide (NO) and prostaglandin (PG)E2, is now considered as a principle cause of most immunological diseases, such as cancer and autoimmunity. Some ginsenosides (e.g., G-Rb1, GRd and G-Rh2) can modulate these phenomena effectively by inhibiting the production of inflammatory mediators through suppressing the activation of nuclear factor (NF)-kB and its upstream signaling cascade.[96]

Toxicity study

The ginseng saponins showed weak toxicities in mice. Especially, Rg1, Rf and Rb1, which contained glucose as a sugar component, were weaker in their toxicities than the rest, which contained arabinose and/or rhamnose. It was also noted that the saponins containing protopanaxadiol as sapogenin were more toxic than those containing protopanaxatriol. All the saponins diminished ACh-

induced contraction of the isolated ileum of the guinea pig. On the other hand high concentrations of Rb 2 caused contraction of the ileum by itself. All of the saponins induced a decrease in heart rate and showed biphasic actions on the blood pressure in rats, while they little affected respiration. They caused blood pressure fall preceded by slight rise. Among them, Rg 1 showed the most prominent action and it produced a blood pressure rise with doses of 30 to 100 mg/kg. The pressor as well as depressor action was not influenced by the pretreatment with any of atropine, diphenhydramine, phentolamine and propranolol. Rg1 and Re showed vasodilator action in dogs, the potencies of which were 1/20 and 1/50 of that of papaverine, respectively. Rc and Rb2 showed very weak vasodilator actions but Rb 1 did not. Among the 7 saponins, Rd, Re and Rb2 showed more potent hemolytic actions than those of the rest and the potencies were proportional to their toxicities. Whereas single administration of Rf, Re and Rd significantly suppressed the conditioned avoidance response, repeated administration of them caused facilitation of the response. On the other hand, Rb 2 always showed very weak suppressant action. Rg 1, Rf, Re and Rd significantly suppressed the fighting of mice induced by foot shock, while Rb1, Rb2 and Re little affected the fighting. All the saponins showed antifatigue action. They markedly increased the movement after compulsory gait and the action was consistent and independent of their action on the movement before compulsory gait. The saponins showed moderate depressant actions on the EEG and the behavior in cats. They were qualitatively similar in their actions, although Rg 1, Re and Rb 2 were more potent than the rest. They also suppressed EEG arousal response induced by electrical stimulation of the mid brain in cats.[97]

Determination of amino acid

A reversed-phase high-performance liquid chromatographic (RP-HPLC) method that allows the determination of several amino acids in primary cultured cortical neurons of rats. The concentration of amino acids was determined by using pre-column derivatization with dansyl chloride and UV-diode array detection. Data show that *Panax ginseng* radix extract (GS) can modulate amino acid release in neurons. The levels of glutamate (Glu), aspartate (Asp), γ-aminobutyric acid (GABA) and glycine (Gly) in the GS-treated groups were higher than in the non-treated groups dose-dependentwise. In this case, Gluand GABA were the most released amino acids (74.43% ± 0.97 and 88.41% ± 4.12 at ginseng dose 0.01 mg/ml after 1 h from treatment, respectively). The values obtained in the determination of the analytical parameters (linearity, precision, limit of detection and accuracy) confirm the quality of the method. The average recoveries for intra and inter-day assay (n = 5) were 101.18 and 102.38 for Asp, 99.35 and 98.44 for Glu, 99.59 and 99.66 for Gly, and 100.06 and 100.37 for GABA. These data proved that the method yields accurate results, with RSD lower than 2.2%. The precision of the method was estimated on the basis of RSD of six injections at two different concentrations of amino acids. This technique is useful in studying the GS-mediated modulation of the dynamic equilibrium of amino acids and neurotransmission in neurons.[98]

SYNERGISTIC ACTIVITIES

Antioxidant activity

Panax ginseng (ginseng) and *Lagerstroemia speciosa* (banaba) were analysed for total antioxidant activity by TEAC assay, superoxide, hydroxyl, hydrogen peroxide and nitric oxide radical scavenging activities as well as total phenolic and flavanoid contents. The calculated results with trolox standard curve, the TEAC value explain the antioxidant potential of the GE overhaul BLE. In superoxide and nitric oxide radical scavenging assays, both GE and BLE showed almost similar range of activities when compared to the reference compounds. BLE was found to be less effective in H_2O_2 and hydroxyl scavenging activities compared to GE. The present study provides an evidence that *Panax ginseng* extract even though having comparatively less amount of flavonoid and phenolic contents than leaf extract of *Lagerstroemia speciosa*, shows potential antioxidant and free radical scavenging activity.[99]

Antimetabolic syndrome

Ginseng-specific saponins (ginsenosides) are considered as the major bioactive compounds for the metabolic activities of ginseng. Berberine from rhizoma coptidis is an oral hypoglycemic agent. It also has anti-obesity and anti-dyslipidemia activities. The action mechanism is related to inhibition of mitochondrial function, stimulation of glycolysis, activation of AMPK pathway, suppression of adipogenesis and induction of low-density lipoprotein (LDL) receptor expression. Bitter melon or bitter gourd (*Momordica charantia*) is able to reduce blood glucose and lipids in both normal and diabetic animals. It may also protect β cells, enhance insulin sensitivity and reduce oxidative stress. Although evidence from animals and humans consistently supports the therapeutic activities of ginseng, berberine and bitter melon, multi-center large-scale clinical trials have not been conducted to evaluate the efficacy and safety of these herbal medicines.[100]

Tonic (adaptogen)

Orally, Panax ginseng is used as an "adaptogen" for increasing resistance to environmental stress and for improving well-being. It is also used for stimulating immune function, improving physical and athletic stamina, improving cognitive function, concentration, memory, and work efficiency. It is also used orally for depression, anxiety, chronic fatigue syndrome (CFS), Pseudomonas infection in cystic fibrosis, chronic bronchitis, breast cancer, ovarian cancer, liver cancer, lung cancer, and skin cancer. Panax ginseng is also used orally for anemia, diabetes, gastritis, neurasthenia, erectile dysfunction, impotence and male fertility, fever,

hangover, and asthma. It is also used orally for bleeding disorders, loss of appetite, vomiting, colitis, dysentery, insomnia, neuralgia, rheumatism, dizziness, headache, convulsions, disorders of pregnancy and childbirth, hot flashes due to menopause, and to slow the aging process. Topically, Panax ginseng is used as part of a multi-ingredient preparation for treating premature ejaculation. In manufacturing, Panax ginseng is used to make soaps, cosmetics, and as a flavoring in beverages.[27-30] Panax ginseng saponins seem to increase serum cortisol concentrations. Panax ginseng might also increase dehydroepiandrosterone sulfate (DHEA-S) levels in women. Panax ginseng appears to stimulate natural-killer cell activity and possibly other immune-system activity. It might also have some antitumor activity. Panax ginseng decreases the production of tumor necrosis factor (TNF), diminish DNA strand breakage, and inhibit the formation of induced skin tumors. There is conflicting research about the antioxidant and free radical scavenging activity of panax ginseng.[101, 13-15, 102]

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