

Panax (Ginseng)—Panacea or Placebo? Molecular and Cellular Basis of its Pharmacological Activity

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Abstract

Introduction: The use of ethnobotanical drugs amongst Asians as complementary medicine is prevalent and is also gaining increasing popularity in the West. The most well known herb traditionally used as a drug is the root of the ginseng species. There are many traditional and anecdotal claims to the therapeutic properties of ginseng. In recent years, there have been systematic efforts to analyse the bioactivities of ginseng saponins. **Methods:** A comprehensive review of published literature covering molecular and cellular research as well as animal and human studies on ginseng and its derivatives. **Results and Conclusion:** Current published data would serve as a framework to understand the pharmacology of ginseng in its entirety, from its molecular action to actual therapeutic effects observed in human use. A new paradigm is emerging whereby the pharmacological effects of traditional herbs such as ginseng can be understood in the light of their polyvalent actions as demonstrated by ginseng saponins with their positive anti-mutagenic, anti-cancer, anti-inflammatory, anti-diabetes and neurovascular effects. With increasing understanding, evidence-based incorporation of traditional herbs as complementary medicine into mainstream medical science can be achieved in the near future.

Ann Acad Med Singapore 2000; 29:42-6

Key words: Adaptogen, Ginsenosides, Scientific evidence, Tonic

Introduction

The dried roots of the herb ginseng spp. (Araliaceae) have been used for centuries in Asian countries such as China, Japan and Korea. The oldest Chinese pharmacopia, *Sheng-nong Ben-cao Jing*, listed ginseng as a tonic with a myriad of effects (anti-aging, liver tonic, vital energy replenishment) and prescribed for ailments ranging from hypertension, cerebrovascular diseases to atherosclerosis. In recent years, ginseng preparations have also seen increasing usage in Western countries like Germany, Switzerland and Russia where it is classified as an adaptogenic drug which indicates a balancing effect to restore the body's equilibrium.¹⁻³ The common name ginseng is a broad term and actually refers to a number of different species such as Korean/Chinese Ginseng (*Panax ginseng*), American Ginseng (*P. quinquefolius*), Japanese Ginseng (*P. japonicus*), Himalayan Ginseng (*P. pseudoginseng*), Siberian Ginseng (*Eleutherococcus senticosus*). However, these ginseng species share many common phyto-metabolites such as alkaloids, phytosterols, amino-acids and saponins.³ From the late 1950s onward, pioneering work undertaken separately by Petkov⁴ and

Brekhman et al⁵ indicated that ginseng extracts, particularly the saponin fractions can stimulate the central nervous system and enhance nonspecific body resistance. However, the key question remains—does ginseng really have specific pharmacological activities as claimed in traditional herbal medicine?

Therefore, this article review a number of molecular and cell studies that assess the bioactivity of ginseng saponins isolated from ginseng spp. roots. Ginseng saponins, also known as ginsenosides, are triterpene glycosides with steroidal structures that are broadly segregated into three major groups—panaxadiol, panaxatriol and oleanolic acid; based on their sapogenins (aglycones) (Fig. 1).⁶⁻⁸ Currently, more than 30 ginsenosides have been isolated from ginseng roots.

Anti-mutagenic Activity

DNA damage in cells are linked to ageing, apoptosis and oncogenesis. The dammarane-type saponin, ginsenoside Rb2 (G-Rb2) has been demonstrated to upregulate the expression of the Cu,Zn-superoxide dismutase (SOD1) gene.⁹ SOD1 is a key enzyme in the quenching of oxygen

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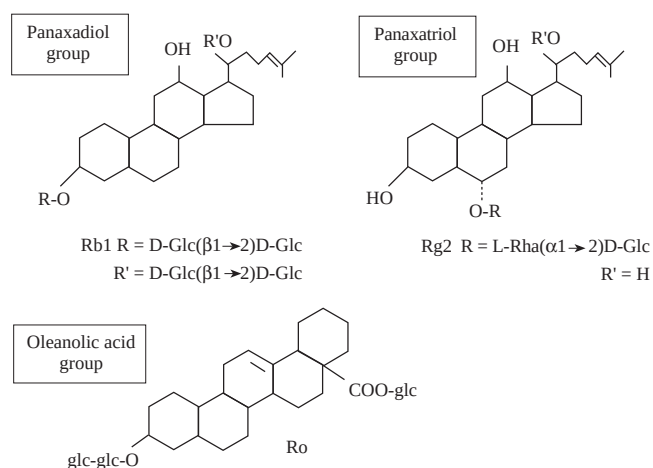


Fig. 1. Structure of ginseng saponins. The ginsenosides are categorised broadly into three main sapogenin groupings—panaxadiol, panaxatriol and oleanolic acid. The nomenclature of individual ginsenosides are based on their side-groups (R , R') together with their sapogenins.

free-radicals.^{10,11} Oxygen free-radicals plays a role in cellular DNA and protein damage and consequently affects the ageing process as well as oxidative-damage related diseases.^{12–15} SOD1 catalyses the dismutation of superoxide radicals (O_2^-) to oxygen and hydrogen peroxide. Ginsenoside Rb2 induces SOD1 expression intracellularly via an indirect mechanism. The SOD1 gene has a number of upstream cis-enhancer elements of which AP1 binding site is one. AP1 is a protein transcription factor. In the presence of G-Rb2, it has been shown that there is a dose-dependent increase in AP1 protein expression and in turn, SOD1 expression leading to increased SOD1 activity and free radical scavenging *in vivo*. Another ginsenoside Rh2 has been shown to suppress the formation of sister chromatid exchanges in human blood lymphocytes.¹⁶ SCE is a biomarker for mutagenic damage and correlates well with the mutation frequency.¹⁷ As such, the specific upregulation of the anti-oxygen radicals enzyme SOD1 as well as the reduction in baseline SCE in normal human cells appear to support the idea that ginseng has anti-ageing/anti-mutagenic effect, or at the very least, cellular DNA-protective effects.

Anti-cancer Activity

Ginseng saponins have also been tested extensively *in vitro* for their anti-proliferative action against mammalian tumour cell lines. Ginsenoside Rh2 has been found to possess anti-cancer activity against the human hepatoma cell line, SK-HEP-1. It was shown that expression of a key cell cycle protein p27^{kip1} was upregulated in the presence of G-Rh2 and this led to blockage of the hepatoma cells at the G1/S phase.¹⁸ Ginsenoside Rh1 and Rh2 can also inhibit proliferation of NIH 3T3 mouse fibroblast cells by modulating the activity of protein kinase C (PKC).¹⁹ PKC is a key kinase involved in protein phosphorylation and the

signal transduction cascade that leads to cell growth and proliferation.^{20–22} The activation of PKC requires diacylglycerol (DAG). DAG in turn is dependent on phospholipase C (PLC) activity. Both Rh1 and Rh2 inhibit PLC activity at concentrations ranging from 10 μM to 100 μM . By reducing PLC activity, the intracellular concentration of the second messenger DAG is decreased. As DAG is an endogenous activator of PKC, the net effect is a reduction in cellular activity of PKC and subsequent inhibition of cell proliferation signal transductions. Similar anti-proliferative activity of G-Rh2 has also been demonstrated in the human breast cancer cell line, MCF-7.²³ In the study, G-Rh2 induced p21 protein expression and concurrently reduced cyclin D thereby downregulating the cyclin-Cdk complex. This leads to decreased phosphorylation of pRb and reduced transcription factor E2F expression. The end-result being the induction of G1 arrest in the cell cycle of MCF-7 cells.

Another approach to anti-cancer treatment is the induction of cell differentiation in neoplastic cells which tend to be less differentiated from normal cells. An example being the use of retinoic acid (RA) in clinical trials to induce differentiation of cancer cells *in vivo*.²⁴ G-Rh1 and G-Rh2 have also been tested *in vitro* for their ability to induce F9 teratocarcinoma stem cells to undergo cell differentiation and loss of tumorigenicity.²⁵ Based on glucocorticoid receptor (GR) recombinant plasmid and glucocorticoid responsive element (GRE)-luciferase report gene construct, it has been shown that the differentiation-inductive effect of G-Rh1 and G-Rh2 on F9 teratocarcinoma cells is mediated through the GR. This GR inductive effect can be augmented with dbcAMP, a secondary messenger in the signal transduction cascade initiated by ligand-bound GR. Alternatively, the ginsenosides agonistic effect on GR can be competitively blocked by RU486, a potent GR antagonist.²⁶

Apoptosis is a genetically-controlled process whereby cells commit suicide. Caspase-3 belongs to a family of proteases that plays a major role in the proteolytic progress of apoptotic cell-death.^{27–29} Ginsenoside Rh2 has also been demonstrated to activate caspase-3 protease via a Bcl-2 insensitive pathway that induced apoptosis in the human hepatoma cell line SK-HEP-1.^{30,31} Ginsenoside Rs3, a diol-type ginseng saponin isolated from Korean red ginseng also trigger apoptosis in SK-HEP-1 albeit via a different mechanism. At doses higher than 5 μM , Rs3 upregulate the protein expression of the tumour suppressor gene, p53, leading to induction of p21^{WAF1} which in turn initiate the process of apoptosis. At doses lower than 5 μM , Rs3 arrests SK-HEP-1 cell cycle at the G1/S transition phase via both cyclins E- and A- associated kinases.³² Similarly, Ginsenoside Rs4 also isolated from *Panax ginseng* C.A. Meyer, selectively elevate the intracellular protein levels

of p53 and p21^{WAF1} and initiate apoptotic cell-death in SK-HEP-1 cells at doses ranging from 5 μ M to 25 μ M.³³

The use of G-Rh2 as an adjuvant to overcome multidrug resistance (MDR) in P388 leukaemia *in vitro* has also been studied.³⁴ The administration of G-Rh2 at 1.5 mg/kg dosage in addition to cytostatic agents such as daunomycin (DAU) and vinblastine (VBL) enhanced the cytotoxicity effect of the drugs against adriamycin (ADM)-resistant P388 leukaemia cells (P388/ADM). P388/ADM develops MDR by reducing intracellular accumulation of the chemotherapeutics by enhanced efflux out of the cells. This active transport of the drugs out of the MDR tumour cells is mediated by the membrane ATPase pump (P-gp). G-Rh2 is postulated to inhibit the function of P-gp, thereby preventing the efflux of the anti-cancer drugs from the MDR cells. This reverses the drug resistance of P388/ADM to anti-cancer chemotherapeutic agents such as DAU VBL.

Anti-inflammatory

The ginsenoside Ro, an oleanane-type ginseng saponin exhibit *in vivo* protective effect against hepatitis in Wistar rats induced by the drugs D-galactosamine (GalN), carbon tetrachloride (CCL4) and α -naphthyl isothiocyanate (ANIT). At doses of 50 mg/kg and 200 mg/kg, G-Rho inhibited the increase in serum glutamic oxaloacetic transaminase (s-GOT) and serum glutamic pyruvic transaminase (s-GPT) in acute hepatic rats. The hepatic-inhibitory effect of G-Ro is even greater than that of a clinical drug glycyrrhizic acid.³⁵ Another *in vivo* study on G-Ro anti-inflammatory effect shows that G-Ro can inhibit drug-induced arthritis in animal models. Physiological effects upon induction of arthritis such as calcium effluence from bone, reduced fibrinolysis and increase in connective tissue in the artery can be prevented by the administration of G-Ro at doses ranging from 10 mg/kg to 200 mg/kg in Wistar rats.³⁶

Anti-diabetes

In streptozotocin-induced diabetes in Wistar rats, G-Rb2 can increase the activity of RNA polymerase I and II which are suppressed under diabetic conditions leading to a certain degree of normalisation in protein synthesis which are compromised in the diabetic Wistar rats.^{37,38} At the same time, intraperitoneally administered G-Rb2 has been shown to restore hepatic ATP levels in streptozotocin-induced diabetic rats.³⁹ Tissue ATP levels *in vivo* are suppressed in diabetic rats compared to normal rats due to impaired energy metabolism brought about by the insulin deficiency as observed in diabetes mellitus.⁴⁰

Neurovascular Effects

Ginsenosides exert cerebro and cardiovascular effects *in*

vivo by modulating the ionic Na⁺ and K⁺ channels. In studies on G-Rg3, the ginsenoside can induce both endothelium-dependent and endothelium-independent relaxation of isolated rat aorta.^{41,42} Although both responses possibly involve tetraethylammonium-sensitive K⁺ channels; the biochemical pathways are different. In endothelium-dependent relaxation of aorta, G-Rg3 activates the tetraethylammonium-sensitive K⁺ channels of the endothelial cells, causing K⁺ efflux and this hyperpolarises the endothelial cells, causes an influx of Ca²⁺ (not mediated by voltage-dependent Ca²⁺ channels).⁴³ The increase in intracellular Ca²⁺ activates nitrate synthase and results in the synthesis and release of nitrate oxide (NO). This causes direct relaxation of the vascular smooth muscle of the blood vessel walls and resultant vasodilation.⁴¹ Another alternative pathway involve endothelium-independent aortic relaxation elicited by G-Rg3. The tetraethylammonium-sensitive K⁺ channels are similarly activated in the smooth muscle cells and this leads to hyperpolarisation of the vascular smooth muscle by K⁺ efflux in low K⁺ solution and inhibition of the voltage-dependent Ca²⁺ influx causing indirect relaxation of the aorta.^{42,44,45}

In a recent study on G-Rg3 and receptor-mediated cation channels, it was shown that G-Rg3 directly antagonises nicotinic acetylcholine receptor-operated cation channels, thereby inhibiting Na⁺ influx and catecholamines (e.g. noradrenaline) secretion in bovine adrenal chromaffin cells.⁴⁶ G-Rg3 also strongly reduced γ -aminobutyric acid-induced catecholamine release from bovine cells.⁴⁷ γ -aminobutyric acid operates the GABA_A receptors, another class of ionotropic receptors similar to the nicotinic receptors. G-Rg3 also inhibited muscarine- and histamine-induced ileum contractions of the guinea-pig by blocking muscarinic acetylcholine and histamine receptors. Total ginsenosides have also been demonstrated to modulate the release of noradrenaline from rat cerebral cortex slices, again possibly via blockage of the Ca²⁺ channels.⁴⁸

Human Studies

Emerging epidemiological and clinical studies also suggest that ginseng intake do exert beneficial pharmacological effects in humans. Notably, the therapeutic effects reported are in the areas of cancer-prevention, anti-hepatitis effect, anti-diabetic effect and adaptogenic effect on general health. In case-control and cohort studies conducted in Korea, it was shown that a significant reduction in risk of non-organ specific cancer development in a dose-responsive manner was associated with increasing frequency and duration of ginseng intake.⁴⁹⁻⁵¹ In accordance with molecular studies that showed anti-hepatitis effect with ginsenosides, a standardised ginseng extract was demonstrated in a clinical trial involving 24 elderly patients

suffering from toxin-induced (alcohol and drugs) chronic liver disease to exert anti-hepatotoxicity effects. Bromsulphthalein retention, blood zinc levels, serum bile acids and gamma-glutamyl transpeptidase levels were significantly modified in comparison to placebo.⁵² In a double-blind, placebo-controlled, 8-week study involving 36 newly diagnosed non-insulin-dependent diabetes mellitus (NIDDM) patients, 200 mg daily dose of ginseng improved glycated haemoglobin and reduced fasting blood glucose (FBG).⁵³ Another double-blind, placebo-controlled study of 227 volunteers receiving an anti-influenza polyvalent vaccine whilst concurrently receiving a standardized ginseng extract or placebo showed that the group receiving ginseng supplementation had a near doubling in natural killer (NK) activity at weeks 8 and 12 compared to the placebo group.⁵⁴ The antibody titres in the ginseng supplementation group also rose by an average of 272 units compared to an average of 171 units in the placebo group which is statistically significant ($P < 0.0001$). On the use of ginseng as a general health tonic or adaptogen, a double-blind, placebo-controlled and randomised quality-of-life study using a standardised 11-item questionnaire was conducted involving 625 patients that received either a multivitamin complex or multivitamin complex supplemented with ginseng extract.⁵⁵ Although both groups reported a significant increase in the quality-of-life index, the increase in index was higher for the group receiving ginseng supplementation with multivitamin complex. This index increment being 11.9 points for the group taking ginseng extract with multivitamins compared to 6.4 points for the group taking multivitamins alone.

Conclusion

Roots of the *Panax* spp. have been used medicinally over the last 5000 years in the Orient. It is interesting to note that the adaptogenic/tonic properties of the ginseng roots show good correlation with the different biochemical actions exhibited by the individual ginsenosides such as G-Ro, G-Rg2, G-Rh1 at the molecular and cellular level. Since the somatic plant tissue of ginseng will contain total ginsenosides of different fractions; the many attributed pharmacological effects of ginseng may arise in part from the *in vivo* pleiotropic action of the ginseng saponins. Recent human clinical trials also appear to correlate with the animal and molecular studies, substantiating the therapeutic effects of ginseng, a herb widely used in traditional medicine. It is tempting to suggest a new paradigm whereby the medicinal use of traditional herbs such as ginseng will see formal incorporation into mainstream medicine in the future as their complex molecular targets and polyvalent mechanisms become clearly elucidated and understood.

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