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Review Article

Ginseng – is there a use in clinical medicine?

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Summary: ***Panax ginseng*** **occupies an important place among the tonic remedies of Oriental medicine. Pharmacological investigations show that crude ginsenosides can increase non-specific resistance of an organism to various untoward influences. The effects of purified derived derivatives have only recently become better studied in immunological and cell growth studies in animals and in man. This has now provided some evidence to suggest that ginseng is a drug that contains many derivatives with different pharmacological properties, which could be useful in clinical medicine.**

Introduction

Ginseng, the root of the arialaceous plant, *Panax ginseng,* has been used for 5000 years in the Orient as a tonic and restorative. Although all parts of the plant contain pharmacologically active ingredients, it is the root that is highly prized. *In vitro* somatic embryogenesis and flowering of embryoids derived from mature root callus of ginseng can be readily induced,[1] but cultivation of the root is long and difficult, taking 6 or 7 years before it is ready for harvesting. Nowadays large scale ginseng cultivation is industrially processed in modern factories in Korea, producing millions of pounds worth of the root in the form of powder, liquid extracts, tablets and capsules, which are sold worldwide. Interest in herbal remedies has not only increased ginseng production manyfold in Europe and America, but has encouraged Western pharmaceutical firms and pharmacologists to investigate its actions and properties.

The history of its clinical usage in the Orient has been to restore and enhance normal well being and not as curative medicine. Brekhman, of the Academy of Sciences in Vladivostok, described it as an 'adaptogen' – a substance that is innocuous, does not impair physiological functions, but helps to increase resistance against noxious or stressful influences of a physical, chemical or biological nature, and in general has a normalizing effect.[2] Although ginseng fulfils some of these criteria, recent reports suggest that side effects of behaviour stimulation and hypertension may occur in high dosage.[3]

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Chemistry

The separation and isolation of ginseng saponins, called ginsenosides, was first reported by Russian and Japanese workers using column and thin layer chromatography. The acccepted nomenclature of the individual saponins named R_x ($x=0$, a, b1, b2, c, d, e, f, g1, g2) is based on the sequence of spots detected after silica gel thin layer chromatography.[4] The chemical structure of these saponins is based upon the tetracyclic triterpenes, protopanaxadiol and protopanaxatriol. The ginsenosides Ra to Rg_2 differ in the number and arrangement of sugar residue, glucose, rhamnose, xylose and arabinose, variously combined with one another and attached to the hydroxyl groups. Modern extraction techniques followed by high pressure liquid chromatography have enabled the analysis and standardization of the saponin content of the ginseng extracts.[5] More recently, the chemical structures of white ginseng (peeled and dried roots) and red ginseng (steamed, ginseng roots without peeling) have been further determined by ^{13}C-NMR, chemical reactions (including methylation analyses) and enzymatic degradations (Figure 1).[6] White ginseng is produced by air-drying the root, while red ginseng is produced by steaming the root followed by drying. Extracts of red and white ginseng contain different ginsenosides.

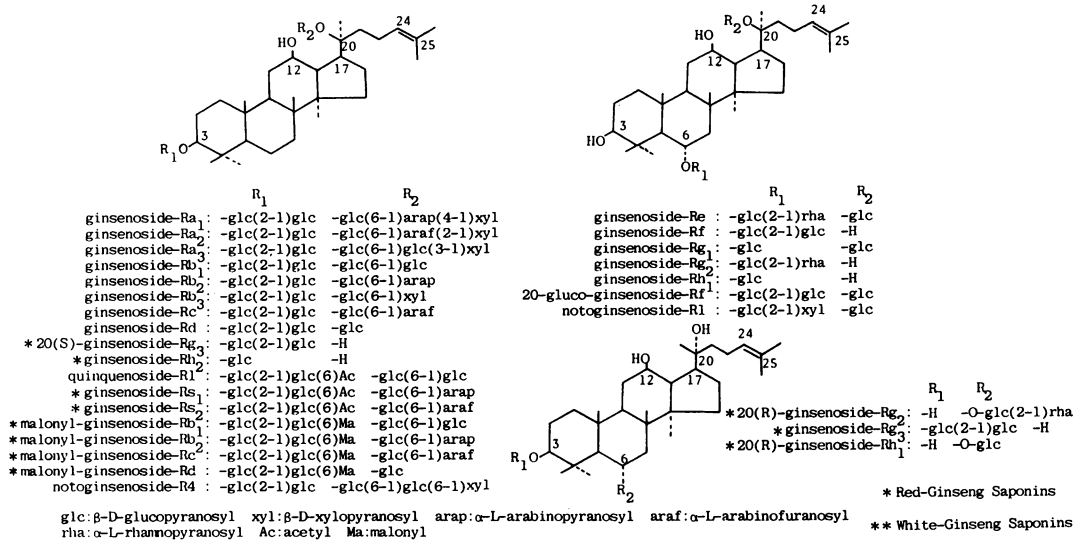

Figure 1 Chemical structure of ginseng.

Pharmacological effects

Whilst subjective effects on well-being have been reproducibly obtained in many reported series, the pharmacological properties of *Panax ginseng* reported in man have been contradictory. In animals, hypertensive and hypotensive effects, histamine and antihistamine-like actions, and stimulatory or depressant activity on the central nervous system have all been described.[7] These contrasting effects may be partially related to the dosage levels employed.[8]

Contradictory reports of the actions of ginseng may also be explained by differences in quantities of the active ginseng components in preparations tested in the past, as crude extracts were generally used.[9] The most active components of ginseng have been identified as saponin substances which possess hormone-like effects and probably account for its anti-fatigue properties. Clinical improvement in diabetic patients given red ginseng powder orally over a 3 month period was reported to be related to the presence of adenosine and an unknown acidic peptide with insulin-like properties.[10] β-Sitosterol, a steroid sapogenin which is absorbed from the gastrointestinal tract and lowers blood cholesterol has also been isolated from ginseng.[11]

The individual ginsenosides can exert opposite pharmacological effects which may explain some contradictory results reported. The main two ginsenosides Rb_1, a protopanaxadiol derivative with 1,2 glycosyl-glucose and 1,6 glycosyl-glucose sugar residues on 3 and 20 positions and Rg_1 a 6,20 diglycoside of protopanaxatriol, have, respectively, suppressive and stimulatory effects upon the central nervous system.[12]

In vivo studies (animals)

Neuropharmacological effects

Animal experiments on the anti-fatigue effects of ginseng were first performed by Brekhman *et al.* in a long-term study in which groups of mice were allowed to swim once every 5 days until exhaustion. Over a 2-month period the average swimming period of the animals given ginseng was double that of the other group.[13] Italian workers reported a consistent anti-fatigue activity in rats and mice following intraperitoneal administration of standardized extracts.[14]

In rats and mice small doses of ginseng extracts (2.5 to 5.0 mg/kg) injected intraperitoneally appeared to increase spontaneous motor activity, while larger doses (40 mg/kg or above) had an inhibitory effect upon the central nervous system.[15] The behaviour response of mice to stress following a dose of ginseng extract of 8 mg/kg/day was also studied by Fulder in 1981. The animals receiving ginseng showed more crouching and less exploratory movements, indicating an exaggeration of the adaptive behaviour responses to stress.[16] In particular, red ginseng potentiated the performance of forced exercise in mice, and delayed the extinction of learning behaviour in stressed mice in a recent control study.[17]

Endocrine effects

The hormone-like effect of these substances was illustrated by changes induced in rats after long-term oral treatment. There was a modest reduction in blood glucose, fall in triglycerides, no change in cholesterol concentration but a striking fall in eosinophils. Histological examination revealed signs of hyperfunction in the supra-optic and paraventricular nuclei of the hypothalamus and hyperplasia of zona fasciculata of adrenals suggesting an induction of ACTH release from the hypophysis. Mediation via the adrenal cortex or the pituitary adrenocortical axis would explain the anti-stress properties of ginseng. Purified ginseng saponins have been shown to increase the adrenal cyclic AMP in intact rats but not in the hypophysectomized animals. Measurements of plasma ACTH by radio-immunoassay and plasma corticosterone by competitive protein binding in rats were made following intraperitoneal administration of ginseng saponin mixtures. A marked response in ACTH excretion coupled with a parallel rise and fall in corticosterone occurred. There was a linear dose response curve between rise in corticosterone from 1 to a maximum 35 μg% and the amount of saponin mixture given from 0.5 to 4 mg/100 g body weight. This response was attenuated by prior treatment with dexamethasone 35 μg/100 g body weight i.p. The isolated ginsenosides Rb_1, Rb_2, Rc, Rd and Re also produced significant rises in plasma corticosterone at doses of 3.5 mg/100 g body weight in rats. The responses could not be explained by induction of epinephrine, insulin or histamine release, and indicate that the ginosenosides stimulate the hypothalamic–hypophyseal system.[18,19]

An oestrogen-like effect of ginseng saponins on vaginal epithelium was recently reported which in the absence of changes in serum oestrogen levels may have arisen from interaction with uterine receptor proteins.[20]

Kimura *et al.* demonstrated a lowering blood sugar and increase in blood insulin levels in alloxan treated diabetic mice.[21]

Biochemical effects

Other reports of their *in vivo* action have, however, not been consistent. Rg_1 was shown to increase DNA, protein and lipid synthesis in rat bone marrow cells[22] and to increase labelled leucine incorporation into serum protein of mice, whereas Rb_1 was inactive.[23] On the other hand, Rb_1 was reported to promote serum protein and RNA synthesis in rats but Rg_1 could not.[24,25]

Anti-inflammatory effects

Earlier studies indicated that the saponins of *Panax ginseng* had anti-inflammatory properties. These properties were measured by the stabilizing action on the heat denaturation of an albumin solution and the suppression of oedema induced by injection of carrageenin into the hind paws of rats. One specific compound identified as C42 H72 O14, after isolation and purification, was shown to produce delayed and prolonged anti-inflammatory effects.[26]

Immunological effects

More recently, the steroid-like properties of the ginseng saponins were demonstrated by modulation of the immune response of mice to influenza virus infection. Total saponins extracted from *Panax ginseng* root when injected intravenously at a dose of 0.2 mg into mice effectively suppressed delayed-type hypersensitivity response to virus and to sheep erythrocytes when given prior to sensitization.[27]

When administered orally in combination with 6-MFA (an interferon-inducing antiviral substance of fungal origin), ginseng extract significantly enhanced the protection of mice against Semliki Forest virus compared to 6-MFA alone.[28]

In vivo studies (man)

Anti-fatigue effects

The tonic effects of ginseng administration over placebo on one hundred young soldiers in Eastern Siberia before a 3 km race showed that the soldiers who had taken ginseng completed the course on average 53 seconds faster than the others.[29] Further experiments on wireless operators and telegraphists for mental concentration and coordination were performed. The individuals on ginseng made fewer mistakes.[30]

In a double-blind study, Sandberg tested the psychomotor and intellectual function of 33 young students by measuring their ability to trace on paper a complex spiral maze and select certain letters from randomized groups of letters according to certain rules. He demonstrated that a single dose of ginseng extract had similar anti-fatigue effects to caffeine.[31]

Fulder studied British nurses in a London hospital doing regular periods of night-duty. Korean white ginseng or an identical placebo in capsule form was given under double-blind conditions to 12 nurses of both sexes on three successive days before night-duty. The nurses taking ginseng felt more

alert and tranquil during their work, and performed better during a test of speed and coordination.[32]

Improved physical performance of 20 top athletes aged 18–20 years from 3 different sports was demonstrated following ginseng administration. This was supported by advantageous changes in functional capacity as measured by blood lactate levels, heart rate and oxygen absorption.[33] A double-blind study of 120 subjects aged 30–60 years also confirmed the stimulatory effect of ginseng and its capacity to increase performance in visual and acoustic reaction tests and in pulmonary function. Significant effects were shown in older men and women (40–60 years) but not in the younger adults.[33]

Adverse effects

Reports of acute hypertension following a short course of ginseng treatment have been described,[3] together with side effects of behaviour stimulation, sleeplessness, diarrhoea,[34] mastalgia[35] and skin eruption in high doses. As far as is known, there are no drug interactions with ginsenosides.[36]

Pharmacological and immunological studies *in vitro* (animals)

Stimulation of DNA synthesis in bone marrow cells of rats was shown following the addition of a *Panax ginseng* extract direct to the incubation medium. At 25 μg/ml synthesis was doubled as measured by the incorporation of ^3H thymidine into DNA. Protein and DNA synthesis were also significantly increased in minced testes of rats using the same ginsenoside fraction at a concentration of 50 μg/ml.[22]

The effect of insulin release in a perfusion system and from isolated pancreatic islets of diabetic mice was potentiated significantly by an isolated hypoglycaemic fraction of the ginseng root (DPG 2–3).[21] Its mode of action was shown to be related to stimulating calcium ionic uptake.[37]

The natural killer cell activity in mice with lung adenoma induced by urethane and benzoapyrene was enhanced by the administration of red ginseng.[38] Similar results of augmentation of natural killer cell activity in mice receiving ginseng extracts have been reported.[39] This group of workers also showed enhancement of humoral (haemagglutinating antibody titre) and cell-mediated immune response based on macrophage migration inhibition test in mice to sheep red blood cells and Semliki Forest virus antigens.

Immunological effects *in vitro* (man)

Until recently, little was known of the local effects of *Panax ginseng* on the immunological system. Chao[40] performed studies with human lymphocytes activated by phytohaemagglutinin or concanavalin A and showed that Rg_1 could promote mitosis at concentrations between 0.3 to 0.5 μg/ml. The ginsenoside Rb_1, however, had the opposite effect inhibiting mitosis and DNA synthesis of stimulated lymphocytes.

We extended these studies to examine whether *Panax ginseng* had any steroid-like activity. The effects of hydrocortisone or *Panax ginseng*, and a combination of hydrocortisone and *Panax ginseng* on phytohaemagglutinin (PHA-P)-induced transformation of peripheral blood lymphocytes were studied in 4 normal healthy adult volunteers. Increasing concentrations of *Panax ginseng* 0.16–1.60 μg/ml caused a dose-related inhibition of PHA-P transformation of lymphocytes. A combination of 500 μg/ml hydrocortisone and 0.80 μg/ml *Panax ginseng* produced a greater suppression of PHA-P stimulation than either drug used alone. This suggests that *Panax ginseng* has a steroid-like effect *in vitro* and may have a potentiating effect with hydrocortisone on suppression of T-cell PHA activation.[41]

There has been a preliminary *in vitro* study on human peripheral blood lymphocytes, that ginseng extract increases natural killer cell activity and antibody-dependent cell cytotoxicity (ADCC).[42]

Further studies need to be done to elucidate whether the action of *Panax ginseng* is truly 'steroid-like'. Our laboratory is currently investigating if the purified extracts of *Panax ginseng* have an effect on blocking immunomodulatory lymphokine pathways. Our results show that Rh_1, Rh_2 and Rd ginsenosides have marked inhibitory effects on interleukin 1 and interleukin 2 activity.[43]

Quality control and future research

There is now sufficient published evidence to suggest that ginseng is a drug.[44] Quality control and standardization of products must, therefore, be made available for further elucidation of the *in vivo* and *in vitro* effects described. A positive result in a controlled study is meaningful, but a negative result must be reviewed against the context of variability of quality of material and does not necessarily imply absence of effect in a sample of adequate quality.[43]

Very recently, growth inhibitory activities of various ginsenosides against some cultured tumour cells have been studied by Odashima *et al.*[45] Ginseno-

side Rh_2 exhibited persistent growth inhibitory effects on B-16 melanoma cell lines. The growth rate recovered on removal of the ginsenoside suggesting a cytostatic effect.

Conclusion

Animals studies have in many instances confirmed the effects of ginseng preparations on man *in vivo*. The reported effects have been mainly beneficial and apparently safe in respect to chronic toxicity. However *ad-libitum* recommendations of ginseng are common in America as dose recommendations are not required. (The US Food and Drug Administration regards ginseng as food). It should be better controlled if serious side effects due to liberal intake are to be avoided.[46] It is important to distinguish between its effects which are measurable without being necessarily symptomatic, such as blood pressure, blood sugar, hormone levels, and those which can be experienced but not easily quantified, such as well-being. Further work should be directed to investigate to what extent *in vitro* evidence is reflected and confirmed *in vivo*.

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