Review paper

Immunotropic and anti-tumor effects of plant adaptogens. I. *Panax ginseng*

EWA SKOPIŃSKA-RÓŻEWSKA

Pathology Department, Biostructure Center, Warsaw Medical University, Poland

Abstract

Panax ginseng is one of the most popular adaptogen and anti-stress plants in Asiatic traditional medicine. The paper presents a brief review of the scientific publications on immunotropic and anti-tumor activities of this plant.

Key words: *adaptogens, Panax ginseng, immunity, tumors.*

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Introduction

The use of medicinal plants is an important part of traditional medicine in many cultures. Especially important is a group of herbs with adaptogenic properties. Extracts prepared from these plants, and some compounds isolated from these extracts increase the ability of an organism to adapt to detrimental environmental factors. Moreover, administration of various plant adaptogens increases mental performance and physical capacity in humans. The beneficial anti-stress action of plant adaptogens is mediated through hypothalamic-pituitary-adrenal (HPA) axis and the sympatho-adrenal-system (SAS) [1]. Experiments performed in mice showed that adaptogens exert a stress-protective effect by modulation of expression of molecular chaperones [2].

Panax ginseng C.A.Meyer (*Araliaceae*) radix is a widely used herbal product in China and other eastern Asian countries, as a tonic and sedative agent. Within the plant genus *Panax* there are several species (*Panax quinquefolius* – the American ginseng, *Panax notoginseng*, *Panax japonicus*, *Panax trifolius* and *Panax vietnamensis*), but the only one with which pharmacological trials have been carried out and which is registered in Pharmacopeia is *Panax ginseng* (Korean *Panax ginseng*). Korean ginseng is found to have such main active compounds as ginsenoside, polyacetylene, acid polysaccharide, anti-oxidative aromatic compound, and insulin-like acid peptides. Korean ginseng roots contain 38 types of ginsenosides (American ginseng contains 19 types only) and also more other active compounds than American ginseng roots [3].

According to legends, ginseng was discovered in the mountains of Manchuria over 5000 years ago and has been used as food for a long time. Most legends are Korean, some Chinese and a few Japanese. For medicinal purposes ginseng has probably been used for over 3000 years and its cultivation probably began 1500 years ago. In ancient times it was as precious as gold and used only by kings and emperors. Traditional Eastern medicine uses ginseng to relieve fatigue and sexual impotence, and as a general antidote to aging. It was believed, that ginseng "strengthens the soul, brightens the eyes, opens the heart, expels evil, benefits understanding, invigorates the body and prolongs life" [4].

Various factors affect the content of active substances in ginseng – most importantly the age of the roots (the best are 6-8 years old) and the conditions of storage and processing. Fresh ginseng roots may be dried in the sun (white ginseng) or steamed (red ginseng and black ginseng). The main active compounds are ginsenosides belonging to the chemical class of triterpene saponins, polyacetylenes (panaxytriol), protopanaxadiol and protopanaxatriol (deglycosylated ginsenoside metabolic derivatives). These ginsenoside metabolic derivatives and panaxytriol have potent inducer activity of quinine reductase, a chemoprotective phase 2 enzyme. Red ginseng contains more active ingredients than the white one, also products of Amadori reaction, arginyl-fructose and arginyl-fructosyl-glucose [5-9].

Effects of ginseng on diabetes

Ginseng has been reported to decrease hyperglycemia in experimental and clinical studies. Korean red ginseng

Correspondence: Ewa Skopińska-Różewska, Department of Pathology Medical University in Warsaw, 5 Chałubińskiego St., 02-004 Warsaw, Poland. Email: ewaskop@hotmail.com

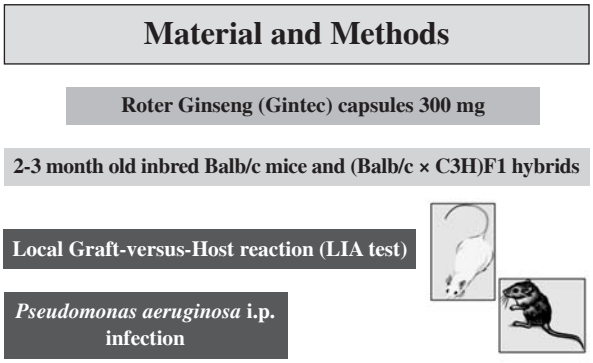

Fig. 1. Material and methods.

improved insulin sensitivity in rats [10] and stimulated insulin release from isolated rat pancreatic islets [11]. In the study of 36 patients with non-insulin-dependent diabetes, the 200 mg dose of Panax ginseng administered for 8 weeks improved fasting glucose levels and glycosylated hemoglobin values [12].

Effects of ginseng on immune system

It was reported that the extract of radix ginseng stimulated the chemotaxis of human leukocytes in vitro, enhanced neutrophiles chemiluminescence and the activity of NK cells [13]. Mice treated with an aquaeous extract of *Panax ginseng* responded with an enhanced SRBC antibody formation and the activity of natural killer (NK) cells [14]. Short-term oral administration of ginseng to mice enhanced natural killer cells activity and appeared to enhance Th-1 type cytokine production [15].

We previously reported the immunomodulatory effect of crude ginseng roots (in the form of ginseng radix flakes and granulated mass of radix) on humoral and cellular immunity in mice [16]. We also presented our results of another study performed on mice with red ginseng extract [17]. Both extracts stimulated *in vivo* various parameters of immunity (production of anti-SRBC antibodies, chemokinetic activity of spleen cells, production of immunological mediators in local graft-versus host reaction). Red ginseng extract have reduced *Pseudomonas aeruginosa* infection in mice. Brief description of some our experiments and their results are presented on Figures 1-7.

Song et al. [18] challenged rats intratracheally with *Pseudomonas aeruginosa* followed by subcutaneous injections of ginseng extract and examined on days 7 and 21. This treatment have modulated the immune system (higher lung IgA, interferon gamma, Il-4 and TNF-alfa, milder lung pathology) in favor of clearing the infection with *P. aeruginosa* in the lungs of rats.

Polysaccharide fraction of *Panax ginseng* exerted *in vitro* and *in vivo* anti-septicaemic activity (*S. aureus* infected mice) by stimulating macrophages. When macrophages were treated with this fraction, phagocytic activity, the level of inflammatory cytokines, and production of nitric oxide and hydrogen peroxide were enhanced. Moreover, cytotoxic activity against B16 melanoma cells was significantly induced. It was demonstrated that *Panax ginseng* induces production of proinflammatory cytokines via toll-like receptor [19-22]. Ginsenosides of *Panax ginseng* have

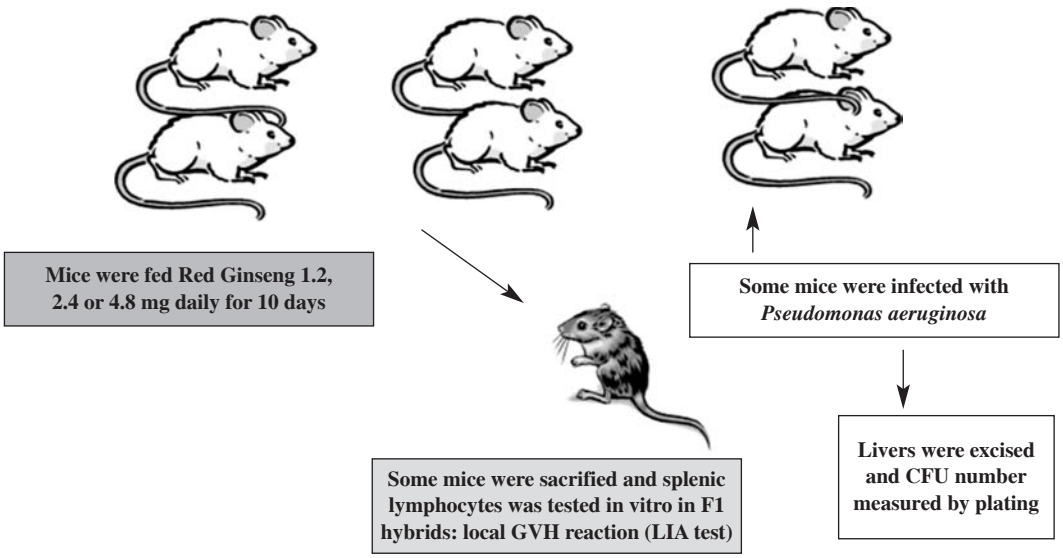

Fig. 2. Scheme of experiments.

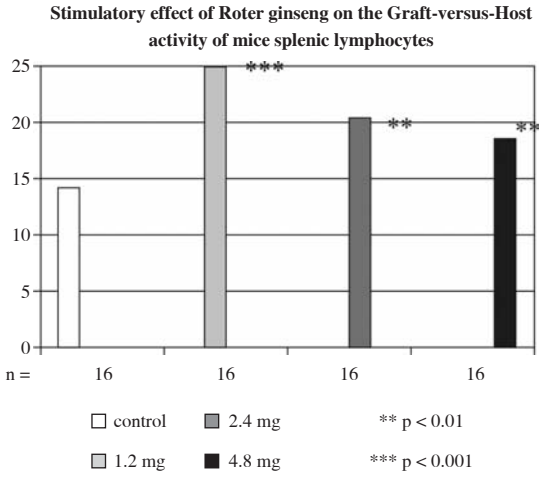

Fig. 3. The effect of Roter ginseng on graft-versus-host reaction.

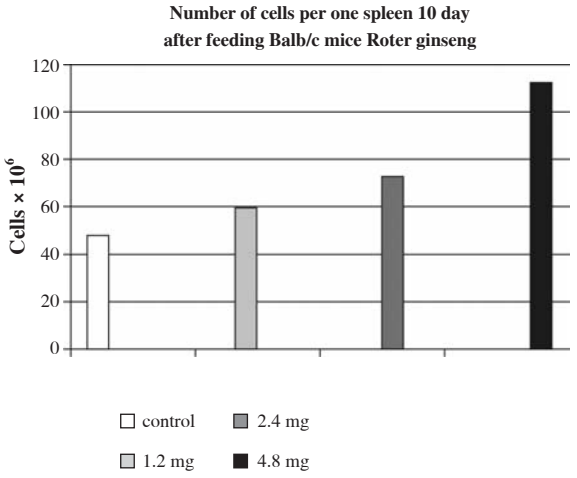

Fig. 4. The effect of Roter ginseng on the number of spleen cells.

demonstrated glucocorticoid-like activities in homeostasis and regulation of immunity. The results of the study of Ling et al. [23] suggest that ginsenosides may reverse partially the dexamethasone-induced down-regulation of glucocorticoid receptor.

In vitro, ginsenosides showed anti-microbial activities toward pathogenic Gram-positive and Gram-negative bacteria and fungi (*Candida albicans*) by disrupting the structure of cell membrane [24, 25].

Clinical studies of healthy volunteers demonstrated that daily administration of 100 mg of standardized *Panax ginseng* extract, Ginsana, enhanced the efficacy of influenza vaccine, increased antibody levels, NK activity, chemotaxis, phagocytosis, total lymphocyte count and number of T helper cells. In patients with acute exacerbation of chronic bronchitis, those treated with antibiotics plus ginseng showed faster bacterial clearance than patients treated with antibiotics alone [26-28]. Beneficial effect of a combination

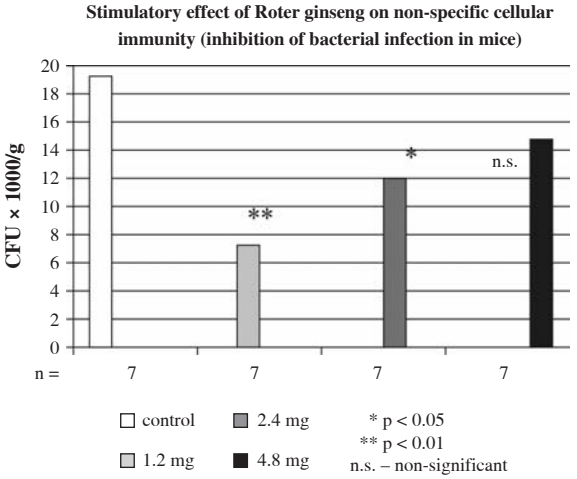

Fig. 5. The effect of Roter ginseng on the bacterial infection in mice.

Feeding mice Roter ginseng gave following effects:

1. **Enhancement of graft-versus host activity of splenic lymphocytes (specific cellular immunity)**
2. **Suppression of bacterial infection by peritoneal macrophages and granulocytes (non-specific cellular immunity)**

Fig. 6. Summary of results.

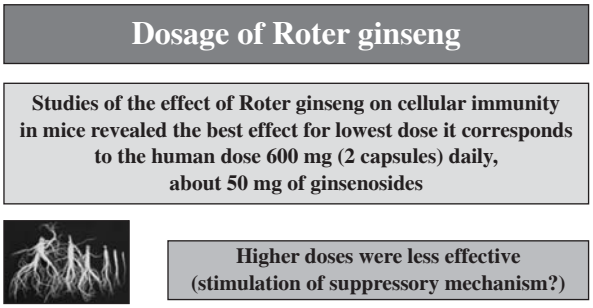

Fig 7. Dosage of Roter ginseng.

of Korean red ginseng and highly active antiretroviral therapy in human immunodeficiency virus type-1 infected patients was also described by Korean authors [29].

Antitumor activity of *Panax ginseng*

Korean investigators performed experiments with 2000 newborn mice to investigate whether *Panax ginseng* inhibited carcinogenesis induced by several chemical carcinogens. Ginsenoside Rg3, Rg5 and Rh2 were found to be active anticarcinogenic compounds [30]. Ginsenoside Rg3 has been found to inhibit the metastasis of experimental ovarian cancer. The inhibitory effect was partially due to inhibition of angiogenesis and MMP-9 [31]. Ginsenoside Rg3 combined with gemcitabine inhibited angiogenesis and growth of lung cancer and improved survival of tumor-bearing mice [32]. The anti-angiogenic effects of ginsenoside Rb1 were demonstrated *in vitro* and *in vivo*. Rb1 suppressed the formation of endothelial tube-like structures through modulation of pigment epithelium – derived factor (PEDF) via estrogen receptor (ER)beta [33]. The sapogenins of two major ginseng saponins inhibited proliferative activity of endothelial cells [34]. *Panax ginseng* C.A.Meyer cultivated in Korea presented non-organ specific cancer-preventive effect due to ginsenoside Rg3, Rg5, and Rh2 [35]. It was also reported that Korean red ginseng extract induced apoptosis and decreased telomerase activity in human leukemia cells [36]. Red ginseng inhibited the recurrence of stage III gastric cancer and showed immunomodulatory activities during post-operative chemotherapy [37]. Ginsenoside Rg1 present in water extract of *Panax ginseng* stimulated angiogenesis *in vitro* and *in vivo*, without increasing VEGF expression [17, 38] what may be important for promoting cardiovascular disease, wound healing and tissue regeneration. The red ginseng has a potent antithrombotic effect *in vivo* due to the anti-platelet activity, which may be beneficial to patients with thrombotic and cardiovascular diseases [39].

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