Acta Pharmacol Sin 2008 Sep; 29 (9): 1103–1108

Invited review

Comparison of the pharmacological effects of *Panax ginseng* and *Panax quinquefolium*

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Key words

Panax ginseng; *Panax quinquefolium*; steaming ginseng; ginsenosides; ginseng saponins; pharmacological effects; chemical components

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Received 2008-07-08
Accepted 2008-07-28

doi: 10.1111/j.1745-7254.2008.00868.x

Abstract

Medical application of *Panax ginseng* was first found in "Shen-Nong Herbal Classic" around 200 AD *Panax quinquefolium* was first introduced in "Essential of Materia Medica" in 1694 in China. The most important bioactive components contained in *P ginseng* and *P quinquefolium* are ginseng saponins (GS). The contents of ginsenoside Rb1, Re, and Rd in *P quinquefolium* are higher than they are in *P ginseng*. In *P ginseng*, the contents of Rg1,Rb2, and Rc are higher than they are in *P quinquefolium*. *P ginseng* had a higher ratio of Rg1: Rb1, and which was lower in *P quinquefolium*. After steaming for several hours, the total GS will decrease. However, some ginsenosides (Rg2, 20R-Rg2, Rg3, Rh1 and Rh2) increase, while others (Rb1, Rb2, Rb3, Rc, Rd, Re, and Rg1) decrease. However, variation, especially in *P quinquefolium*, is high. *P ginseng* and *P quinquefolium* are general tonics and adaptogens. Rg1 and Rb1 enhance central nervous system (CNS) activities, but the effect of the latter is weaker. Thus, for the higher contents of Rg1, *P ginseng* is a stimulant, whereas the Rb1 contents of *P quinquefolium* are mainly calming to the CNS. Re, Rg1, panaxan A and B from *P ginseng are* good for diabetes. Re and Rg1 enhance angiogenesis, whereas Rb1, Rg3 and Rh2 inhibit it. Rh2, an antitumor agent, can be obtained from Rb1 by steaming. The content of Re in *P quinquefolium* are higher than in *P ginseng* by 3-4 times. The vasorelax, antioxidant, antihyperlipidemic, and angiogenic effects of Re are reported. Thus, for the CNS "hot," wound healing and hypoglycemic effects, *P ginseng* is better than *P quinquefolium*. For anticancer effects, *P quinquefolium* is better.

Introduction

It can be hypothesized that in ancient times people in Manchuria and Siberia sought nourishment by digging out the root of *Panax ginseng* from beneath the ground. As people migrated to North America, they also found the value of *Panax quinquefolium*. The Chinese character of ginseng appeared in the Jia-Gu-Wen (Oracle bone script) of Shang Dynasty (1600-1100 BC)[1,2]. A detailed description of the medical applications of *P ginseng* was found in "Shen-Nong-Ben-Cao-Jing" (Shen-Nong Herbal Classic) which was edited around 200 AD. *Panax quinquefolium* was first introduced by Wang Ang of the Qing Dynasty in "Essential of Materia Medica" in 1694, and again by Wu Yi LUO in the "New Compilation of Materia Medica" in 1757[3].

Red *P ginseng* is recognized in traditional Chinese medicine (TCM) as being warm in nature, sweet or slightly bitter in flavor. It delivers to the spleen, lung and heart meridians, and is used to invigorate "Qi" and strengthen "Qi" in the spleen and lung, and promote the production of body fluids to quench thirst, tranquilize the mind and improve intelligence. *P ginseng* is used for the treatment of

collapse due to "Qi" deficiency, fatigue, poor appetite, diarrhea, shortness of breath, feeble pulse, spontaneous perspiration, diabetes, febrile diseases, amnesia, insomnia and impotence. It is believed that ginseng roots with human body shapes are spirited. *P quinquefolium* is also recognized as a sweet, slightly bitter in flavor, but cold in nature, and delivers to the lung, heart as *P ginseng* does; not to spleen but to kidney meridians. Used as supplement "Qi", drives out body heat and promotes the production of body fluids. It is also used for the treatment of cough with dyspnea and bloody sputum, dysphoria, fatigue and thirst[3,4]. In brief, red *P ginseng* is stimulating and invigorates "Yang", whereas *P quinquefolium* is calming and nourishing "Yin".

Chemistry

Factors affecting the bioactive component(s) in plants Pharmacological effects of herbal drugs depend on the type of bioactive component(s) and the quantity that is used. However, many variables such as soil, fertilization, temperature, rainfall, distance between or among the cultured plants and age, will determine the quality of the herb. Again, the contents of bioactive components in leaf, flower, bud, seed, berry, stem, and each part of the root (main root, side root, rootlet) are different. Of course, the process changes the chemical composition, and the sensitivity of the method and instruments used are other variables. The total ginseng soponins (GS) contents increase in accordance with the age of *P ginseng*. In 10-, 6-, or 4-year-old *P ginseng*, the contents of GS in the main root are 4.99%-5.89%, 3.80%-5.22%, and 2.60%, respectively[5,6]. Thus *P ginseng* and *P quinquefolium* below 4 years of cultivation is not suitable for harvest[7].

Classification of ginseng saponins (GS) Until now, more than 80 GS have been isolated from *Panax taxa*. They are classified as protopanaxadiols (PPD), such as Ra1, Ra2, Ra3, Rb1, Rh2, Rb3, Rc, Rd, 20(S)-Rg3, Rb2, quinoquenosides (Q)-R1, Rs1, Rs2, malonyls (MA)-Rb1, MA-Rb2, MA-Rc, MA-Rd, Rg3, etc., protopanaxatriols (PPT), such as Re, Rf, Rg1, Rg2, Rh1, 20-glucopyranosyl (Glc)-Rf, r-R1, 20R-Rg2, 20R-Rh1, etc., oleanolic acid (R_o), and ocotillol (P-F_{11},R15) types[1,2,8-10].

Contents of GS in *P ginseng* Total GS content is highest in the flower buds (8.4%-26.4%), then berry (8.25%-21.8%), crown (4.29%-17.4%), rootlet (9.2%-12.3%), side root (6.5%-12%), leaf (7.6%-12.6%), seed bud (3.19%) stem (2.1%), and seed (0.7%), respectively[6]. After several hours of steaming, the quantity of GS will decrease by more than 30%. Some GS are increased (Rg2, 20R-Rg2, Rg3, Rh1 and Rh2), whereas some are decreased (Rb1, Rb2, Rb3, Rc, Rd, Re and Rg1) [11].

The contents of PPD, PPT and oleanolic acid types of ginsenosides in *P ginseng* root are 1.64%-3.16%, 0.72%-1.07% and 0.38%-0.61%, respectively. The PPD type of ginsenosides content in *P ginseng* is highest in rootlet (6.67%), then crown (5.38%), berry (3.95%), flower buds (3.56%), leaf (2.93%), main root (2.57%), stem (0.75%), and seed (0.26%), respectively[5].

Among PPD types of ginsenosides, the contents of malonyl (M)-Rb1 (0.82%) are highest, then Rb1 (0.47%), M-Rb2 (0.41%), M-Rc1 (0.30%), Rc (0.26%), Rb2 (0.21%), Rd (0.15%) and M-Rd (0.12%), respectively. In PPT types of ginsenosides, the highest are Rg1 (0.17%), then Re (0.15%) and Rf (0.05%), respectively in the root of *P ginseng*. In another study, it was shown that the contents of the PPD type of ginsenosides (2.57%-6.67%) in *P ginseng* root are higher than the PPT type of ginsenosides (1.23%), and in other parts (except the seed) contents have higher PPT type ginsenosides (1.55%-7.78%) than PPD type ginsenosides (0.75%-3.95%)[10].

Contents of GS in *P quinquefolium* The total GS contents in *P quinquefolium* root also increases in accordance with age. The total GS in wild grown *P quinquefolium* root is higher than in cultivated ones. However, there is a high variation of total GS of individual wild roots ranging from 1% to 15%[12], and there is no apparent relationship between age and total GS content for roots 5 years or older[13]. The total GS contents in *P quinquefolium* is highest in the flower buds (12%-16%), then leaf (10%-16%), berry (10%-12%), crown (8.76%) and stem(2.18%)[10]. The contents of ginsenoside Rb1 (1.51%), Re (0.89%), Rd (0.77%), in *P quinquefolium* is about 3, 6 and 5 times higher than they are in *P ginseng* [10]. Rb1>Re>Rg1=Rc>Rd, and these five ginsenosides account for more than 70% of total GS in *P quinquefolium*[2,7,14]. Thus, *P ginseng* had a high ratio of Rg1:Rb1 and *P quinquefolium* had a low ratio of Rg1:Rb1[15,16]. Rb1, Rb2, Rc, Rd, Re, Rf, Rg1, Rg2, Rg3, Rh1, and Ro are common constituents in white and red *P ginseng*, whereas 20(R)-Rg2, 20(S)-Rg3, 20(R)-Rh1, and Rh2 are the characteristic components of red *P ginseng*[6].

The anticancer ginsenosides Rg3 and Rh2 can be obtained from Rc and Rb1 under thermal processes[11,17]. 24(R)-pseudoginsenoside F11 content is 0.1% in *P quinquefolium*, and only 0.0001% in *P ginseng*. Rf content in *P ginseng* root is more than 0.021%, whereas the contents of 24(R)-pseudoginsenoside F11 is 1/700 of Rf[18].

Polysaccharides and glycopeptides identified from *P ginseng* GS polysaccharides and glycoproteins are the most important bioactive compositions in *P ginseng* and *P quinquefolium*. Besides purified polysaccharides GH-1 (M_r

4,500) and G-H-2 (M_r 5,300), 21 panaxan (A-U) M_r ranging from 2,500 to 1,300,000 have been identified[19]. Glycopeptide named *P ginseng* P-21 (average M_r 6,000)[20] and glycoprotein PA and PB are obtained from the root of *P ginseng*. Polysaccharides from stem (5AUH, 5AUL, 5NUH, 5NUL), leaf (GL-P1, II, IV) and berry (F1-F4) [21,22] have also been identified from *P ginseng* by investigators in China.

From *P quinquefolium* cultivated in China, 11%-19% dry material can be obtained by water extraction. *P quinquefolium* contains 52.3%-65.0% sugars and its starch content is 24.9%-28.9%[23]. The contents of proteins and enzymes in *P quinquefolium* are about 11.00%-12.38%[24].

Pharmacology

Panax ginseng and *P quinquefolium* have for a long time been among the most popular botanic products in the world. Market demand depends on the high reputation of the empirical history of the plants, so evidence-based data about their safety from pre-clinical and clinical studies provides many benefits.

General effects of *P ginseng* and *P quinquefolium* *Panax ginseng* and *P quinquefolium* are general tonics and adaptogens to maintain the body's resistance to adverse factors and homeostasis, including enhanced physical and sexual functions, general vitality, anti-stress and anti-aging. Such effects are caused by acting on the hypothalamic-pituitary-adrenal axis and hypothalamic-pituitary-gonadal axis, or more basically by antioxidative effects, or enhanced oxygen and cellular glucose uptake.

Effects of ginsenosides on the CNS The synthesis, release, reuptake, and metabolism of neurotransmitters, neuromodulators, neuromediators, and neurotrophic factors by neurons, astrocytes, microglia, or immune cells control the activities of the CNS. Free radical formation and oxidative stress will damage neurons. Rg1 and Rb1 enhance CNS activities, but the effect of the latter is weaker[25], sometimes even having an inhibitory effect on the CNS. *P ginseng* root has a higher ratio of Rg1 (0.27%) to Rb1 (0.5%-1.5%) content, and *P quinquefolium* has a lower ratio of of Rg1 (0.133%) to Rb1 (4.94%) content. Thus, *P ginseng* maintains both stimulatory and inhibitory effects, and in some situations even has a "hot" or stimulating effect, while *P quinquefolium* is "cool" or calming to the CNS. The protective effects of Rb1, Rg1, Rg3 and Rh2 on neurodegeneration are well reported[26-30].

Effects on the cardiovascular system The homeostasis of blood pressure is controlled by stroke volume, heart rate, and resistance of blood vessels. However it is also controlled by the CNS, sympathetic and parasympathetic nervous systems, intrinsic and extrinsic control mechanisms of the heart, volume of body fluids, renal function, renin-angiotensin system, nitric oxide, endothelins, and products of inflammation and platelet aggregation, and may also affect atherosclerosis or ischemia-reperfusion induced tissue or organ damage. Contrary to popular belief, it has been found that the water extract of *P ginseng* caused hypotensive effects in conscious rats[31]. This was also confirmed in conscious hypertensive rats[32], and essential hypertensive patients[33,34]. Rg1 and Rg3 relax vascular smooth muscle[35-37], and inhibit endothelin production[38]; Therefore, not only is it the antihypertensive component in *P ginseng*, but it also has anti-atherosclerotic effects and promotes wound healing[39]. Lipophic fraction from red *P ginseng* inhibits platelet aggregation[40]. *P ginseng* Rb1, Re[41-44], and Rg1[29] enhance recovery of the brain, heart and other ischemia injury to organs.

Effects on immune system, inflammation and allergy Inflammation is the response to infections, antibodies, chemical or physical injuries. However, exaggerated and prolonged inflammation will induce adverse consequences. Interactions of selectin, complement factor C5a, platelet-activating factor, cytokines, interleukin-1, tumor necrosis factor and eicosanoids LTB4 are important factors in affecting the adhesion of leukocytes and platelets to the sites of inflammation. Rb1 inhibits leukotriene release, Rg1 increases the T-helper cell and stimulates immune activity in the aged, polysaccharide and PPT type ginsenosides enhance interferon production, phagocytosis, natural killer cells, B and T cells[44]. Rb1, Rg1 and Rg3 inhibit cytokine production, inhibit COX-2 gene expression, inhibit histamine release, stabilize neutrophils and lymphocytes[29,42,45-47].

Anticancer effects Besides the practice of cancer medicine, drugs for restoring bone marrow function, induction of tumor differentiation, inhibition of angiogenesis, biological response modifiers, and cancer prevention are all under investigation. *P ginseng* has radioprotective effects. Chronic intake of *P ginseng* decreased the incidence of lung, gastric, liver and colorectal tumors. Rh2 and Rg3 suppressed breast, prostate, liver and intestinal cancer[11,48-53]. The anti-proliferative effects of petroleum ether extract of *P ginseng* in cultured human renal cell carcinoma cell lines were demonstrated; even its potency was weaker than partially purified *P ginseng* preparation, panaxydol, and some as panazynol[54]. Therefore, additive or synergic anticancer effects of different bioactive components in *P ginseng* must occur. We emphasize here that the contents of the polyacetylene compound in *P ginseng* are higher than

in *P quinquefolium*.

Hypoglycemic effect Red *P ginseng*, ginseng berry, leaf of *P quinquefolium*, and Re are antidiabetics. Rg1 increases the number of insulin receptors. Panaxan A and B glycans from *P ginseng* root increases plasma insulin levels and enhance insulin sensitivity[55,66].

Phytoestrogenic effects Red *P ginseng* helps postmenopausal woman with climacteric syndromes, such as fatigue, insomnia and depression, and Rb1, Re, Rg1, Rh1 are active components[67-70]. Re activates eNOS through estrogen activation, then promotes vasodilatation[71]. However, Rb1 promotes nitric oxide production in human aortic endothelial cells through androgen receptors[72].

Effects of ginsenosides on angiogenesis In atherosclerosis, diabetic retinopathy, psoriasis, rheumatoid arthritis, and tumor, there is excessive angiogenesis. On the contrary, alopecia, Alzheimer's disease, chronic wound, critical limb ischemia, hypertension, ischemic coronary artery, ulceration are related to the decrease of angiogenesis. Re[73] and Rg1[38,74] enhance angiogenesis. Rb1[38], Rg3, and Rh2[74] inhibit angiogenesis. Rb1, Rb2, Rc and Rg3 inhibit tumor angiogenesis and metastasis. Rg1 inhibits microglia proliferation[75-79]. As pointed out by Fan *et al*, Rg1 leads to angiogenesis, whereas Rb1 exerts an opposing effect[38]. Rb1 and Rg1 are major bioactive components in *P quinquefolium* and *P ginseng*, respectively. Therefore Rg1 or *P ginseng* is better for wound healing than *P quinquefolium*.

Conclusion

Total GS of *P ginseng* and *P quinquefolium* is decreased during the steaming process. However, the formation of red dextran increases the stability of bioactive components and increases the contents of Rg3, Rh1, Rh2 and 20(*R*)-Rg2, in *P ginseng*, and Rh1, Rg2, 20(*R*)-Rg2, Rg3 and Rh2 in *P quinquefolium*. The contents of individual components are more important than the total ginsenosides. Different bioactivities of *P ginseng* and *P quinquefolium* were confirmed not only clinically, but also at cellular and molecular levels recently. The contents of each bioactive component, its efficacy or/and potency will affect the pharmacological effects. However, as other botanic products, the problem of inconsistency of quality of *P ginseng* and *P quinquefolium* is also serious.

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