

## Invited review

**Comparison of the pharmacological effects of *Panax ginseng* and *Panax quinquefolium***Chieh-fu CHEN<sup>1,5</sup>, Wen-fei CHIOU<sup>2</sup>, Jun-tian ZHANG<sup>3,4</sup>

<sup>1</sup>Institute of Pharmacology, National Yang-Ming University, Taipei, China; <sup>2</sup>National Research Institute of Chinese Medicine, Taipei, China; <sup>3</sup>Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing 100050, China; <sup>4</sup>Peking Union Medical College, Beijing 100050, China

**Key words**

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

<sup>5</sup>Correspondence to Chieh-fu CHEN.

Phn 886-937-839-528.

Fax 886-2-2365-4243.

E-mail chiehfu.chen@gmail.com

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)<sup>[1,2]</sup>. 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<sup>[3]</sup>.

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<sup>[3,4]</sup>. 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 saponins (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<sup>[5,6]</sup>. Thus *P ginseng* and *P quinquefolium* below 4 years of cultivation is not suitable for harvest<sup>[7]</sup>.

**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 (Ro), and ocotillol (P-F11, R15) types<sup>[1,2,8-10]</sup>.

**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<sup>[6]</sup>. 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)<sup>[11]</sup>.

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<sup>[5]</sup>.

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%)<sup>[10]</sup>.

**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%<sup>[12]</sup>, and there is no apparent relationship between age and total GS content for roots 5 years or older<sup>[13]</sup>. 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%)<sup>[10]</sup>. 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*<sup>[10]</sup>. Rb1>Re>Rg1=Rc>Rd, and these five ginsenosides account for more than 70% of total GS in *P quinquefolium*<sup>[2,7,14]</sup>. Thus, *P ginseng* had a high ratio of Rg1:Rb1 and *P quinquefolium* had a low ratio of Rg1:Rb1<sup>[15,16]</sup>. 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*<sup>[6]</sup>.

The anticancer ginsenosides Rg3 and Rh2 can be obtained from Rc and Rb1 under thermal processes<sup>[11,17]</sup>. 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<sup>[18]</sup>.

**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*,

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<sup>[19]</sup>. Glycopeptide named *P. ginseng* P-21 (average  $M_r$  6,000)<sup>[20]</sup> 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)<sup>[21,22]</sup> 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%<sup>[23]</sup>. The contents of proteins and enzymes in *P. quinquefolium* are about 11.00%-12.38%<sup>[24]</sup>.

## 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<sup>[25]</sup>, 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 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<sup>[26-30]</sup>.

**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<sup>[31]</sup>. This was also confirmed in conscious hypertensive rats<sup>[32]</sup>, and essential hypertensive patients<sup>[33,34]</sup>. Rg1 and Rg3 relax vascular smooth muscle<sup>[35-37]</sup>, and inhibit endothelin production<sup>[38]</sup>. Therefore, not only is it the antihypertensive component in *P. ginseng*, but it also has anti-atherosclerotic effects and promotes wound healing<sup>[39]</sup>. Lipophilic fraction from red *P. ginseng* inhibits platelet aggregation<sup>[40]</sup>. *P. ginseng* Rb1, Re<sup>[41-44]</sup>, and Rg1<sup>[29]</sup> 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<sup>[44]</sup>. Rb1, Rg1 and Rg3 inhibit cytokine production, inhibit COX-2 gene expression, inhibit histamine release, stabilize neutrophils and lymphocytes<sup>[29,42,45-47]</sup>.

**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<sup>[11,48-53]</sup>. 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<sup>[54]</sup>. 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 glycanes from *P. ginseng* root increases plasma insulin levels and enhance insulin sensitivity<sup>[55,66]</sup>.

**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<sup>[67-70]</sup>. Re activates eNOS through estrogen activation, then promotes vasodilatation<sup>[71]</sup>. However, Rb1 promotes nitric oxide production in human aortic endothelial cells through androgen receptors<sup>[72]</sup>.

**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<sup>[73]</sup> and Rg1<sup>[38,74]</sup> enhance angiogenesis. Rb1<sup>[38]</sup>, Rg3, and Rh2<sup>[74]</sup> inhibit angiogenesis. Rb1, Rb2, Rc and Rg3 inhibit tumor angiogenesis and metastasis. Rg1 inhibits microglia proliferation<sup>[75-79]</sup>. As pointed out by Fan *et al*, Rg1 leads to angiogenesis, whereas Rb1 exerts an opposing effect<sup>[38]</sup>. 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.

## References

- Zhao HZ, editor. Cyclopedia of *Panax ginseng* and American ginseng. Hong Kong: Rong-Zhai Publishers; 1998. p 9. [In Chinese]
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2006. p. 587-91. [In Chinese]
- Kiangsu Institute of Modern Medicine. Encyclopedia of Chinese Drug. Shanghai: Shanghai Scientific Technical Publication; 1977. p 29-36, 850-1. [In Chinese]
- State Administration of Traditional Chinese Medicine of the People's Republic of China. Zhong-Hua-Ben-Cao, Condensed edition. Shanghai: Shanghai Scientific Technical Publication; 1996. p 1269-74, p 1301-5. [In Chinese]
- Zhao HZ, editor. Cyclopedia of *Panax ginseng* and American ginseng. Hong Kong: Rong-Zhai Publishers; 1998. p 249. [In Chinese]
- Zhao HZ, editor. Cyclopedia of *Panax ginseng* and American ginseng. Hong Kong: Rong-Zhai Publishers; 1998. p 223, p 231. [In Chinese]
- Court WA, Reynolds LB, Hendel JG. Influence of root age on the concentration of ginsenosides of American ginseng (*Panax quinquefolium*). Can J Plant Sci 1996; 76: 853-5.
- Tanaka O, Sakai R. Saponins of *Ginseng* and related plants. In: Herz W, Grisebach H (Editors). Progress in chemistry of organic natural products. Vienna: Springer-Verlag, 1984. p 1-76.
- Yang CR, Zhou J, Tanaka O. Chemotaxonomic studies and the utilization of *Panax* species. Acta Bot Yunnanica 1988 Suppl. 1: 47-62. [In Chinese]
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2006. p 486-7. [In Chinese]
- Wang CZ, Aung HH, Ni M, Wu JA, Tong R, Wicks S, *et al*. Red American ginseng: ginsenoside constituents and antiproliferative activities of heat-processed *Panax quinquefolium* roots. Planta Med 2007; 73: 669-74.
- Assinewe VA, Baum BR, Gagnon D, Arnason JT. Phytochemistry of wild populations of *Panax quinquefolium* (North American ginseng). J Agric Food Chem 2003; 51: 4549-53.
- Schlag EM, McIntosh MS. Ginsenoside content and variation among and within American ginseng (*Panax quinquefolium* L.) populations. Phytochemistry 2006; 67: 1510-9.
- Wills RBH, Du XW, Stuart DI. Changes in ginsenosides in Australian-grown American ginseng plants (*Panax quinquefolium* L.). Aust J Exp Agric 2002; 42: 1119-23.
- Cui JF. Identification and quantification of ginsenosides in various commercial ginseng preparations. Eur J Pharmacol Sci 1995; 3: 77-85.
- Ma YC, Luo M, Mally L, Doucer M. Distribution and proportion of major ginsenosides and quality control of ginseng products. Chin J Med Chem 1996; 6: 11-21.
- Popovich DG, Kitts DD. Generation of ginsenosides Rg3 and Rh2 from North American ginseng. Phytochemistry 2004; 65: 337-44.
- Li WK, Gu CG, Zhang HJ, Awang DVC, Fitzloff JF, Fong HHS, *et al*. Use of high-performance liquid chromatography-tandem mass spectrometry to distinguish *Panax ginseng* L.A. Meyer (Asian ginseng) and *Panax quinquefolium* L. (North American ginseng). Anal Chem 2000; 72: 5417-22.
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2002. p 547-553. [In Chinese]
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2002. p 544. [In Chinese]
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2002. p 554, p 555. [In Chinese]
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2002. p 546. [In Chinese]
- Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chi-

- nese Agriculture Sciencetech Press; 2002. p 557. [In Chinese]
- 24 Li FY, editor. *Panax ginseng* and American ginseng. Beijing: Chinese Agriculture Sciencetech Press; 2002. p 577. [In Chinese]
  - 25 Chang Y, Huang WJ, Tien LT, Wang SJ. Ginsenosides Rg1 and Rb1 enhance glutamate release through activation of protein kinase A in rat cerebrocortical nerve terminals (synaptosomes). *Eur J Pharmacol* 2008; 578: 28–36.
  - 26 Zhang JT, Chui DH, Chen CF, editors. The chemistry metabolism and biological activities of ginseng. Beijing: Chemical Industry Press; 2006.
  - 27 Nah SY, Kim DH, Rhim H. Ginsenosides: are any of them candidates for drugs acting on the central nervous system? *J Compil* 2007; 13: 381–404.
  - 28 Tian JW, Fu FH, Geng MY, Jiang YT, Yang JX, Jiang WL, *et al*. Neuroprotective effect of 20(s)-ginsenoside Rg3 on cerebral ischemia in rats. *Neurosci Lett* 2005; 374: 92–7.
  - 29 Wu CF, Bi XL, Yang JY, Zhan JY, Dong YX, Wang JH, *et al*. Differential effects of ginsenosides on NO and TNF-alpha production by LPS-activated N9 microglia. *Intern Immunopharmacol* 2007; 7: 312–20.
  - 30 Radad K, Gille G, Liu LL, Rausch WD. Use of ginseng in medicine with emphasis on neurodegenerative disorders. *J Pharmacol Sci* 2006; 100: 175–86.
  - 31 Chow SY, Chen CF, Hu WS. Pharmacological studies on Chinese herbs with potential hypotensive, analgesic and/or antipyretic effects. *Natl Sci Coun Month* 1976; 4: 2341–4. [In Chinese]
  - 32 Jeon BH, Kim CS, Park KS, Lee JW, Park JB, Kim KJ, *et al*. Effect of Korea red ginseng on the blood pressure in conscious hypertensive rats. *Gen Pharmacol* 2000; 35: 135–41.
  - 33 Han KH, Choe SC, Kim HS, Sohn DW, Nam KY, Oh BH, *et al*. Effect of red ginseng on blood pressure in patients with essential hypertension and white coat hypertension. *Am J Chin Med* 1998; 26: 199–209.
  - 34 Sung J, Han KH, Zo JH, Park HJ, Kim CH, Oh BH. Effects of red ginseng upon vascular endothelial function in patients with essential hypertension. *Am J Chin Med* 2000; 28: 205–16.
  - 35 Kang SY, Schini-Kerth VB, Kim ND. Ginsenosides of the protopanaxatriol group cause endothelium-dependent relaxation in the rat aorta. *Life Sci* 1995; 56: 1577–86.
  - 36 Chen X. Cardiovascular protection by ginsenosides and their nitric oxide releasing action. *Clin Exp Pharmacol Physiol* 1996; 23:728–32.
  - 37 Kim DN, Kim EM, Kang KW, Cho MK, Choi SY, Kim SG. Ginsenoside Rg3 inhibits phenylephrine-induced vascular contraction through induction of nitric oxide synthase. *Br J Pharmacol* 2003; 140: 661–70.
  - 38 Nakajima S, Uchiyama Y, Yoshida K, Mizukawa H, Haruki E. The effect of ginseng radix rubra on human vascular endothelial cells. *Am J Chin Med* 1998; 26: 365–73.
  - 39 Sengupta S, Toh SA, Sellers LA, Skepper JN, Koolwijk P, Leung HW, *et al*. Modulating angiogenesis: the yin and the yang in ginseng. *Circulation* 2004; 110: 1219–25.
  - 40 Park HJ, Lee JH, Song YB, Park KH. Effects of dietary supplementation of lipophilic fraction from *Panax ginseng* on cGMP and cAMP in rat platelets and on blood coagulation. *Biol Pharm Bull* 1996; 19: 1434–9.
  - 41 Lim J H, Wen TC, Matsuda S, Tanaka J, Maeda N, Peng H, *et al*. Protection of ischaemic hippocampal neuron by ginsenosides Rb1, a main ingredient of ginseng root. *Neurosci Res* 1997; 28: 191–200.
  - 42 Liu ZX, Liu XC. Effect of ginsenoside Rb1 and Re on cardiomyocyte apoptosis after ischemia and reperfusion in rats. *Chin J Histochem Cytochem* 2002; 11: 374–7. [In Chinese]
  - 43 Smolinsk AT, Pestka JJ. Modulation of lipopolysaccharide-induced proinflammatory cytokine production *in vitro* and *in vivo* by the herbal constituents apigenin (chamomile), ginsenoside Rb(1)(ginseng) and parthenolide (feverfew). *Food Chem Toxicol* 2003; 41: 1381–90.
  - 44 Sun K, Wang CS, Guo J, Horie Y, Fang SP, Wang F, *et al*. Protective effects of ginsenoside Rb1, ginsenoside Rg1, and notoginsenoside R1 on lipopolysaccharide-induced microcirculatory disturbance in rat mesentery. *Life Sci* 2007; 81: 509–18.
  - 45 Ro JY, Ahn YS, Kim KH. Inhibitory effect of ginsenoside on the mediator release in the guinea pig lung mast cells activated by specific antigen-antibody reactions. *Int J Immunopharmacol* 1998; 20: 625–41.
  - 46 Keum YS, Han SS, Chun KS, Park KK, Park JH, Lee SK *et al*. Inhibitory effects of the ginsenoside Rg3 on phorbol ester-induced cyclooxygenase-2 expression, NF-kappaB activation and tumor promotion. *Mutat Res* 2003; 523–524: 75–8.
  - 47 Park EK, Shin YW, Lee HU, Kim SS, Lee YC, Lee BY, *et al*. Inhibitory effect of ginsenoside Rb1 and compound K on NO and prostaglandin E2 biosynthesis of RAW 264.7 cells induced by lipopolysaccharide. *Biol Pharm Bull* 2005; 28: 652–6.
  - 48 Shin HR, Kim JY, Yun TK, Morgan G, Vainio H. The cancer-preventive potential of *Panax ginseng*: a review of human and experimental evidence. *Cancer Causes Control* 2000; 11: 565–76.
  - 49 Yun TK, Lee YS, Lee YH, Kim SI, Yun HY. Anticarcinogenic effect of *Panax ginseng* C.A. Meyer and identification of active compounds. *J Korean Med Sci* 2001; 16 Suppl: S6–18.
  - 50 Popovich DG, Kitts DD. Structure-function relationship exists for ginsenosides in reducing cell proliferation and inducing apoptosis in the human leukemia (THP-1) cell line. *Arch Biochem Biophys* 2002; 406: 1–8.
  - 51 Popovich DG, Kitts DD. Ginsenosides can inhibit proliferation and induce apoptosis in cultured leukemia and intestinal cells but effects vary according to the structure of the compounds. *FASEB J* 2003; 17: A762.
  - 52 Helms S. Cancer prevention and therapeutics: *Panax ginseng*. *Alter Med Rev* 2004; 9: 259–74.
  - 53 Yoo HH, Yokozawa T, Satoh A, Kang KS, Kim HY. Effects of ginseng on the proliferation of human lung fibroblasts. *Am J Chin Med* 2006; 34: 137–46.
  - 54 Sohn JW, Lee CH, Chung DJ, Park SH, Kim IS, Hwang WI. Effect of petroleum of *Panax ginseng* roots on proliferation and cell cycle progression of human renal cell carcinoma cells. *Exp Mol Med* 1998; 30: 47–51.
  - 55 Suzuki Y, Hikino H. Mechanisms of hypoglycaemic activity of panaxans A and B, glycans of *Panax ginseng* roots: effects on plasma level, secretion, sensitivity and binding of insulin in mice. *Phytother Res* 1989; 3: 20–4.
  - 56 Takaku T, Kameda K, Matsuura Y, Sekiya K, Okuda H. Studies on insulin-like substances in Korea red ginseng. *Planta Med* 1990; 56: 27–30.
  - 57 Tchilian EZ, Zhelezarov IE, Hadjivanova CI. Effect of ginsenoside Rg1 on insulin binding in mice liver and membranes. *Phytother Res* 1991; 5: 46–8.
  - 58 Sotaniemi EA, Haapakoski E, Rautio A. Ginseng therapy in non-

- insulin dependent diabetic patients. *Diabetes Care* 1995; 18: 1373–5.
- 59 Attele AS, Zhou YP, Xie JT, Wu JA, Zhang L, Dey L, *et al*. Antidiabetic effects of *Panax ginseng* berry extract and the identification of an effective component. *Diabetes* 2002; 5: 1851–8.
- 60 Xie JT, Zhou YP, Dey L, Attele AS, Wu JA, Gu M, *et al*. Ginseng berry reduces blood glucose and body weight in db/db mice. *Phyto-medicine* 2002; 9: 254–8.
- 61 Dey L, Xie JT, Wang A, Wu J, Maleckar SA, Yuan CS. Antihyperglycemic effects of ginseng: comparison between root and berry. *Phyto-medicine* 2003; 10: 600–5.
- 62 Xie JT, Mehandale SR, Wang A, Han AH, Wu JA, Osinski J, *et al*. American ginseng leaf: ginsenoside analysis and hypoglycemic activity. *Pharmacol Review* 2004; 49: 113–17.
- 63 Xie JT, Mehandale SR, Li X, Quigg K, Wang X, Wang CZ, *et al*. Antidiabetic effect of ginsenoside Re in db/db mice. *Biochim Biophys Acta* 2005; 1740: 319–25.
- 64 Xie JT, Mehandale S, Yuan CS. Ginseng and diabetes. *Am J Chin Med* 2005; 33: 397–404.
- 65 Cho WCS, Chang WS, Lee SKW, Leung AWN, Cheng CHK, Yue KKM. Ginsenoside Re of *Panax ginseng* possesses significant antioxidant and antihyperlipidemic efficacies in streptozotocin-induced diabetic rats. *Eur J Pharmacol* 2006; 550: 173–9.
- 66 Cho WC, Yip TT, Chung WS, Lee SK, Leung AW, Cheng CH, *et al*. Altered expression of serum protein in ginsenoside Re-treated diabetic rats detected by SELDI-TOF MS. *J Ethnopharmacol* 2006; 108: 272–9.
- 67 Chan RY, Chen WF, Guo DA, Wong MS. Estrogen-like activity of ginsenoside Rg1 derived from *Panax notoginseng*. *J Clin Endocrinol Metab* 2002; 87: 3691–5.
- 68 Lee Y, Jin Y, Lin W, Ji S, Choi S, Jang S, *et al*. Ginsenoside-Rh1, a component of ginseng saponin, activates estrogen receptor in human breast carcinoma MCF-7 cells. *J Steroid Biochem Mol Biol* 2003; 84: 463–8.
- 69 Cho J, Park W, Lee S, Ahn W, Lee Y. Ginsenoside-Rb1 from *Panax ginseng* C.A. Meyer activates estrogen receptor- $\alpha$  and  $\beta$ , independent of ligand binding. *J Clin Endocrinol Metab* 2004; 89: 3510–15.
- 70 Bae EA, Shin JE, Kim DH. Metabolism of ginsenoside Re by human intestinal microflora and its estrogenic effect. *Biol Pharm Bull* 2005; 28: 1903–8.
- 71 Nakaya Y, Mawatari K, Takahashi A, Harada N, Hata A, Yasui S. The phytoestrogen ginsenoside Re activates potassium channels of vascular smooth muscle cells through PI3K/Akt and nitric oxide pathways. *J Med Invest* 2007; 54: 381–4.
- 72 Yu J, Eto M, Akishita M, Kaneko A, Ouchi Y, Okahe T. Signaling pathway of nitric oxide production induced by ginsenoside Rb1 in human aortic endothelial cells: A possible involvement of androgen receptor. *Biochem Biophys Res Commun* 2007; 353: 764–9.
- 73 Huang YC, Chen CT, Chen SC, Lai PH, Liang HC, Chang Y, *et al*. A natural compound (ginsenoside Re) isolated from *Panax ginseng* as a novel angiogenic agent for tissue regeneration. *Pharm Res* 2005; 22: 636–46.
- 74 Yue PY, Mak NK, Cheng YK, Leung KW, Ng TB, Fan DTP, *et al*. Pharmacogenomics and the Yin/Yang actions of ginseng: antitumor, angiomodulating and steroid-like activities of ginsenosides. *Chin Med* 2007; 2: 6.
- 75 Sato K, Mochizuki M, Saiki I, Yoo YC, Samukawa K, Azuma I. Inhibition of tumor angiogenesis and metastasis by a saponin of *Panax ginseng*, ginsenoside-Rb2. *Biol Pharm Bull* 1994; 17: 635–9.
- 76 Mochizuki M, Yoo YC, Matsuzawa K, Sato K, Saiki I, Tono-oka S, *et al*. Inhibitory effect of tumor metastasis in mice by saponins, ginsenoside-Rb2, 20(R)-and 20(S)-ginsenoside-Rg3, of red ginseng. *Biol Pharm Bull* 1995; 18: 1197–202.
- 77 Shinkai K, Akedo H, Mukai M, Imamura F, Isoai A, Kobayashi M, *et al*. Inhibition of *in vitro* tumor cell invasion by ginsenoside Rg3. *Jpn J Cancer Res* 1996; 87: 357–62.
- 78 Tao H, Yao M, Zou S, Zhao D, Qiu H. Effect of angiogenesis inhibitor Rg3 on the growth and metastasis of gastric cancer in SCID mice. *Zhoughua Waikhe Zazhi* 2002; 40: 606–8. [In Chinese]
- 79 Kang XM, Zhang QY, Tong DD, Zhao W. Experimental study on anti-angiogenesis in mice with Lewis lung carcinoma by low-dose of cyclophosphamide combined with ginsenoside Rg3. *Zhongguo Zhongxiyi Jiehe Zazhi* 2002; 25: 730–3. [In Chinese]