

Phytochemical and pharmacology effect of *Panax notoginseng*

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ARTICLE INFO

Article history:

Received on: 01/07/2016

Revised on: 22/07/2016

Accepted on: 11/08/2016

Available online: 30/08/2016

Key words:

Panax notoginseng,
antioxidant,
antiinflammation,
antithrombotic,
phytochemical.

ABSTRACT

Panax notoginseng has been shown beneficial effects on the cardiovascular system and traditionally used to prevent cerebral ischemia. It has haemostatic, antioxidant, hypolipidaemic, hepatoprotective, renoprotective and estrogen-like activities. The phytochemical compositions of the *Panax notoginseng* are mainly saponins, which belong to protopanaxatriol and protopanaxadiol group. Furthermore, *Panax notoginseng* also has some compounds such as notoginsenoide, flavonoids, phytosteroid. The present review focuses on phytochemical and important pharmacology effect of *Panax notoginseng* including antioxidant, antiinflammation and antithrombotic activities.

INTRODUCTION

Panax notoginseng (Burk.) F. H. Chen (Araliaceae) is a medicinal plant. It is distributed throughout the southwest of China, Japan, Burma, Nepal and Vietnam. This plant belongs to the same family and genus as *P. ginseng*. The root of *Panax notoginseng* is normally harvested in autumn before flowering, after three years of growth. After harvesting, the roots are cleaned, divided into main root, branch root and rhizome then dried under the sun or with artificial heating at low temperatures (Wang *et al.*, 2008). *Panax notoginseng* has sweet and slightly bitter in flavour, slightly warm in nature. This plant is usually applied to treat various kinds of bleeding and pains due to blood stasis (Yang *et al.*, 2014). The figure 1 shows the whole plant and root of *Panax notoginseng*. In this review we summarize some

characteristics of phytochemical and pharmacology effect of the *Panax notoginseng*.



Fig. 1: Whole plant and root of *Panax notoginseng*.

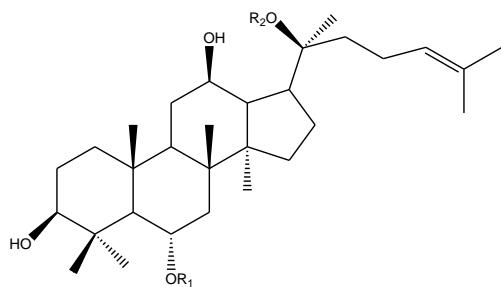
Chemical constituents of *Panax notoginseng*

The phytochemical constituents of *Panax notoginseng* are complex, consisting of various saponins, amino acids, polyacetylenes, volatile oils, polysaccharides and flavonoids. The dammarane-type saponins achieves to 12% of the total root content. These are the main bioactive compounds of the root with many beneficial pharmacology effects.

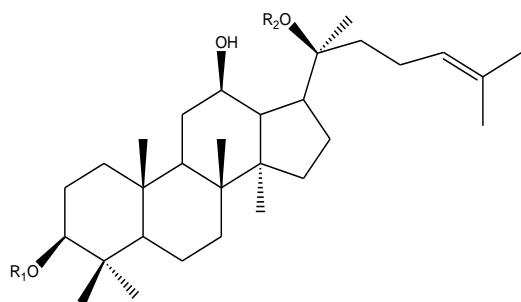
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Panax notoginseng has higher percentage of total saponins compared to *P. ginseng* and *P. quinquefolium*. Its saponins compose various ginsenosides and notoginsenosides. Many of these ginsenosides in the root are also presented in other *Panax* species such as *P. ginseng* and *P. quinquefolium*. Actually, there are more than 30 ginsenosides which have been isolated. The saponins are classified into three main classes based on their aglycones—protopanaxadiol (e.g. ginsenosides Rb1, Rb2, Rc, Rd), protopanaxatriol (e.g. ginsenosides Rg1, Re, Rf) and oleanolic acid (e.g. ginsenoside Ro) (Kim, 2012). Other group of saponins, notoginsenosides, including notoginsenosides R1 to R4, R6 to R9 notoginsenosides A to N, notoginsenosides Fa, Fc and Fe, have been isolated from *Panax notoginseng* (Yoshikawa *et al.*, 2001). Some of saponins in *Panax notoginseng* are presented in figure 2.

Protopanaxatriol (R₁, R₂ = H)

Saponins	R ₁	R ₂
Ginsenoside Rg1	-Glc	-Glc
Ginsenoside Re	-Glc ²⁻¹ Rha	-Glc
Ginsenoside Rf	-Glc ²⁻¹ Glc	-H
Notoginsenoside R ₁	-Glc ²⁻¹ Xyl	-Glc
Notoginsenoside R ₂	-Glc ²⁻¹ Xyl	-H
Notoginsenoside R ₃	-Glc	-Glc ⁶⁻¹ Glc
Notoginsenoside R ₆	-Glc	-Glc ⁶⁻¹ Glc (α)

Protopanaxadiol (R₁, R₂ = H)

Saponins	R ₁	R ₂
Ginsenoside Rb1	-Glc ²⁻¹ Glc	-Glc ⁶⁻¹ Glc
Ginsenoside Rb2	-Glc ²⁻¹ Glc	-Glc ⁶⁻¹ Ara(p)
Ginsenoside Rb3	-Glc ²⁻¹ Glc	-Glc ⁶⁻¹ Xyl(p)
Ginsenoside Rc	-Glc ²⁻¹ Glc	-Glc ⁶⁻¹ Ara(f)
Ginsenoside Rd	-Glc ²⁻¹ Glc	-Glc
Notoginsenoside R ₄	-Glc ²⁻¹ Glc	-Glc ⁶⁻¹ Glc ⁶⁻¹ Xyl
Notoginsenoside Fa	-Glc ²⁻¹ Glc ²⁻¹ Xyl	-Glc ⁶⁻¹ Glc
Notoginsenoside Fc	-Glc ²⁻¹ Glc ²⁻¹ Xyl	-Glc ⁶⁻¹ Xyl
Notoginsenoside Fe	-Glc	-Glc ⁶⁻¹ Ara(f)

Fig. 2: Chemical structures of some saponins. Abbreviations: Glc, glucose; Ara(f), arabinose in furanose form; Ara(p), arabinose in pyranose form; Rha, rhamnose; Xyl, xylose (Jiang, 2007)

Dencichine (β -N-oxalyl-L- α , β -diaminopropionic acid) is an important and bioactive amino acid and presented in *Panax notoginseng*. It has strong haemostatic activity (Long *et al.*, 1996). *Panax notoginseng* also presents some types of amino acids, such as aspartic acid, glutamic acid, arginine, lysine and leucine. The total amount of amino acids arises about 7.73%. Trilinolein, a triacylglycerol with three linoleate residues, is another important compound that was found. It has protective effects against cardiovascular diseases by reducing thrombogenicity, arrhythmias, increasing erythrocyte deformability and counteract free radical damages (Chan *et al.*, 2002). Some polyacetylenes including panaxynol, panaxydol and panaxytriol have also been isolated in *Panax notoginseng*. These compounds have showed cytotoxic, antiplatelet and anti inflammatory activities. Other compounds such as, notoginsenic acid betasophoroside, was isolated also from the roots. Various polysaccharides, such as sanchinan-A, arabinogalactan, were isolated from *Panax notoginseng* and have strong immunostimulatory effects (Yoshikawa *et al.*, 1997). A small chitinase-like antifungal protein whose molecular weight of 15 kDa was found in the root of this plant. Moreover, *Panax notoginseng* contains a series of sesquiterpenes essential oils and some of them have been identified as α -guaiene, β -guaiene, and octadecane (Zhu *et al.*, 2005). Some flavonoids including quercetin, kaempferol, β -sitosterol, stigmasterol, daucosterol also are presented in this medicinal plant (Wang *et al.*, 2006).

Pharmacological activities of *Panax notoginseng*

The *Panax notoginseng* have many different traditional uses. The raw form is officially recognized in Chinese medicine for its haemostatic and cardiovascular properties, such as arrest bleeding, disperse blood clots, improve blood circulation, disperse bruises, cause subsidence of swelling and alleviate pain.

Its well-known haemostatic effect has been studied scientifically (Fan *et al.*, 2005). Several beneficial cardiovascular effects were shown. Animal studies have shown that *Panax notoginseng* extracts decreased blood pressure and peripheral vascular resistance. It increases coronary blood flow, treats experimental myocardial ischemia, alleviates angina pectoris, increases cardiac contractility and, may have anti-arrhythmic effects as well as helps in craniocerebral trauma (Wang *et al.*, 2006). Other reported pharmacological activities of raw *Panax notoginseng* extracts and its total saponins include reduction of blood viscosity, inhibition of platelet aggregations (Wang *et al.*, 2004), anti-inflammatory and analgesic effects (Rhule *et al.*, 2006), retardation of the progress of early diabetic nephropathy, immunological adjuvant activities (Sun *et al.*, 2006), prevention of liver fibrosis and hepatic microvascular dysfunction (Park *et al.*, 2005). Furthermore, the anti-carcinogenic and anti-proliferative activities of the roots of *Panax notoginseng* have been reported (Lam *et al.*, 2001). Notoginsenoside R1, one of the distinct saponins which were presented in *Panax notoginseng*, has been found. It helps increase the fibrinolytic potential in cultured endothelial and smooth muscle cells, counteract endotoxin-

induced activation of endothelial cells and to inhibit TNF-alpha-induced PAI-1 production in human aortic smooth muscle cells (Zhang *et al.*, 2006).

Antioxidant activity

Reactive oxygen species (ROS), such as superoxide anion, hydroxyl radicals and hydrogen peroxide, are chemically reactive molecules derived from oxygen. They are generated in living organisms as by-products through many metabolic pathways. ROS can readily react with and oxidize most biomolecular including carbohydrates, proteins, lipids and DNA whereby increase evidence that accumulation of ROS in biological system causes oxidative damage to tissue that affects cellular integrity and functions. Oxidative damage caused by ROS has been frequently proposed to be associated with the pathogenesis of various diseases and health problems such as aging, arthritis, cancer, inflammation and heart diseases in human body. Consequently, antioxidants that can neutralize directly ROS attacks and terminate free radical-mediated oxidative reaction would have beneficial activities in protecting the human body from such diseases.

The development of atherosclerosis involves the infiltration of low-density lipoprotein (LDL) particles and monocytes into the vascular intima. Oxidation modified LDL, but not native LDL, has been shown like a potent chemo-attractant for circulating monocytes. ROS are also thought to mediate the injury to the myocardium brought about by ischemia and reperfusion. Various ROS scavengers have been shown to reduce this damage during myocardial ischemia/reperfusion, and some of which play clinical role in certain situations. The protective effect of certain dietary constituents is believed to be via antioxidant-mediated resistance to oxidative damage to key biomolecular, including DNA and polyunsaturated fatty acids, reducing the development of diseases, such as cancer or atherosclerosis. *Panax notoginseng* showed activity in decreasing total cholesterol, triglycerides and fibrinogenemia in rats (Cicero *et al.*, 2003).

The *in vitro* antioxidant activities of extract of *Panax notoginseng* were evaluated with different antioxidant testing systems. *Panax notoginseng* exhibited strong ferrous ion chelating activity and high scavenging activities against hydrogen peroxide, hydroxyl radicals, and a weak activity against superoxide anion and DPPH free radicals. These antioxidant properties of *Panax notoginseng* seem to be one of the reasons that they are effective in the prevention and treatment of vascular diseases (Zhao *et al.*, 2006).

Anti-inflammatory activity

Inflammation involving the innate and adaptive immune systems is a normal response to infection. The inflammatory response is simply characterized by involving redness, swelling, heat and pain, which are classic symptoms from the three major events in inflammation. These events are vasodilatation, increasing capillary permeability and influx of phagocytes from the capillaries into the damaged tissue to attack pathogens.

Inflammation allows immune cells to quickly and efficiently travel to sites of infection, at which they can target and eradicate pathogens. However, when allowed to continue without controlled, inflammation results in autoimmune or autoinflammatory disorders, neurodegenerative disease, or cancer. Inflammation is a dynamic process with proinflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and vascular endothelial growth factor (VEGF) playing central roles (Dinarello, 2010). During chronic inflammation, pro-inflammatory molecules, such as cytokines, cyclooxygenase 2 (COX-2) inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and NF- κ B are upregulated. There are many natural and synthetic agents that are currently used in the treatment of inflammatory diseases. In spite of this, there is still a constant search for better agents to treat inflammation. There are some studies reported the anti-inflammatory activity of *Panax notoginseng*. *Panax notoginseng* exerts anti-inflammatory effects related to the inhibition of neutrophil functions including degranulation, superoxide generation and leukotriene B4 production, and reduced nitric oxide NO and prostaglandin PGE2 production, which could be due to a decreased expression of iNOS and COX-2. In addition, *Panax notoginseng* significantly reduced mouse paw edema induced by carrageenan (Jin *et al.*, 2007). Flower of *Panax notoginseng* extract significantly inhibited the productions of NO, PGE2, TNF- α and IL-1 β in on the LPS stimulated RAW264.7 cells. In addition, flower of *Panax notoginseng* extract suppressed the mRNA and protein expressions of iNOS, COX-2, TNF- α and IL-1 β in LPS-stimulated RAW264.7 cells. The molecular mechanism of flower of *Panax notoginseng* extract-mediated attenuation in RAW264.7 cells has close a relationship to suppressing the phosphorylation of MAPK molecules such as ERK1/2, JNK and p38 MAPK, and the translocation of NF- κ B p65 subunit into nuclear (Jung *et al.*, 2009).

Trilinolein from *Panax notoginseng* inhibited significantly nitric oxide (NO), tumor necrosis factor (TNF- α), interleukin-1 (IL-1 β), and IL-6 production in a manner concentration-dependent in a model of lipopolysaccharide (LPS)-stimulated mouse macrophage (RAW264.7). It also blocked the protein expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), nuclear factor- κ B (NF- κ B), I κ B α , and mitogen-activated protein kinases (MAPKs). In the anti-inflammatory test, trilinolein decreased the paw edema after carrageenan administration in paw edema (Huang *et al.*, 2014).

Notoginsenoside R1, a main bioactive component from *Panax notoginseng* showed capacity to alleviate the severity of dextran sulfate sodium-induced colitis in mice by decreasing the activity of myeloperoxidase, the production of cytokines, the expression of proinflammatory genes, and the phosphorylation of I κ B kinase, I κ B α , and p65 in the colon (Zhang *et al.*, 2015).

Panaxatriol saponins, the main constituents extracted from *Panax notoginseng* has been shown to be an effective agent in the protection against Parkinson's disease. Panaxatriol saponins provided neuroprotection against the loss of dopaminergic neurons and behavioral by including enhancing antioxidant activity, acting

as neurotrophic factor, modulating inflammation and inhibiting mitochondria-mediated apoptosis impairment caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a agent-induced neuronal death. Panaxatriol saponins could suppress the MPTP-mediated neuronal death by increasing thioredoxin-1 expression, suppressing cyclooxygenase-2 over-expression and inhibiting mitochondria-mediated apoptosis (Luo *et al.*, 2011).

Microglial cells activation increased neurotoxicity through the production of pro-inflammatory and cytotoxic mediators in mixed neuron-glial cultures stimulated with either toll like receptor (TLR) ligands (LPS), cytokines (TNF α or IFN γ) glutamate, Nmethyl-D-aspartate (NMDA), or β -amyloid (A β). Activation of microglial cells in the central nervous system may initially be intended to protect neurons; however, activation of these cells and inflammatory products derived from them has been implicated in various disease states. Effects of extract of *Panax notoginseng* on TLR ligand-and IFN γ -induced activation in N9 and EOC20 microglial cells lines were investigated. *Panax notoginseng* suppressed microglial activation by reduced expression of accessory molecules (CD40 and CD86), decreased production of inflammatory mediators (IL-6 and TNF- α), and diminished release of antibacterial products (nitric oxide). *Panax notoginseng* and some ginsenosides such as Rb1, Rg1, or Re may be of therapeutic benefit in treating or preventing neurodegenerative diseases such as multiple sclerosis and Parkinson's disease (Beamer *et al.*, 2012).

Antithrombotic activity

Platelets play a central role in the haemostatic process and are similarly involved in the pathological process thrombosis. They are small discoid cells derived from megakaryocytes in the bone marrow and circulate in the blood. Under normal conditions, they neither adhere to each other nor other circulating endothelial cells. When the blood vessels are damaged, subendothelial cells are exposed and platelets adhere to the disrupted surface. This adhesion is mediated by collagen and von Willebrand factor (vWF) on the subendothelial surface. Phospholipase A2 enzyme is also activated to produce a variety of prostaglandins and thromboxane.

Raw *Panax notoginseng* has been traditionally used as a haemostatic to arrest internal and external bleeding, reduce swelling and pain, as well as to disperse blood clots, eliminate blood stasis and promote blood circulation. Studies also showed that raw *Panax notoginseng* has other useful pharmacological activities on cardiovascular related diseases such as lower blood cholesterol, reduce blood pressure, treatment of coronary heart diseases, cardiac infarction and angina pectoris. *Panax notoginseng* (200 mg/kg i.p. x 1d or x 3d) significantly inhibited abnormal increases of platelet aggregation and platelet adhesiveness in rats subjected to permanent occlusion of the middle cerebral artery. Platelet aggregation induced by ADP in vitro was also inhibited by *Panax notoginseng* in a concentration-related manner. Furthermore, *Panax notoginseng* could increase the fluidity of platelet membranes (Ma *et al.*, 1998). Fibrinolysis

is an integral part of the coagulation cascades. It can be regulated by the plasminogen activator (PA) and PA inhibitor (PAI-1). Impaired fibrinolysis and high plasma PAI-1 concentrations are associated with an increasing risk of cardiovascular disease. Notoginsenoside R1 has been demonstrated to upregulate tissue-type PA (tPA) without affecting urokinase-type PA (uPA) and PAI-1 via increasing tPA mRNA in cultured human umbilical vein endothelial cells, while notoginsenoside R1 also could decrease PAI-1 activity via increasing complex formation between tPA and PAI-1. This saponin could also increase the production of tPA and uPA in cultured human pulmonary artery smooth muscle cells, and inhibit TNF- α induced PAI-1 overexpression in VSMCs by suppressing ERK and protein kinase B signaling pathways (Zhang *et al.*, 1994, Kohler *et al.*, 2000). Increase in plasmatic fibrinogen is regarded as a risk factor of cardiovascular disease and *Panax notoginseng* has been found to significantly lower the level of fibrinogen in rat models (Cicero *et al.*, 2003).

CONCLUSION

The chemical components from *Panax notoginseng* have been studied and the largest class of bioactive components is saponins. Pharmacological effects of *Panax notoginseng* have been proven in many studies. It has shown many beneficial effects for health, including antioxidant, anti-inflammatory and antithrombotic activities. Therefore, it is important now to study how to apply *Panax notoginseng* to modern pharmaceutical dosage form for more convenience usage to patients.

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How to cite this article:

Tung BT, Hai NT. Phytochemical and pharmacology effect of *Panax notoginseng*. *J App Pharm Sci*, 2016; 6 (08): 174-178.