



Boletín Latinoamericano y del Caribe de  
Plantas Medicinales y Aromáticas

ISSN: 0717-7917

editor.blacpma@usach.cl

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Chile

Sousa BRAZ, Alessandra de; F. Melo DINIZ, Margareth de Fátima; Nóbrega de ALMEIDA, Reinaldo  
Recent advances in the use of Panax ginseng as an analgesic: a systematic review  
Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas, vol. 8, núm. 3, mayo,  
2009, pp. 188-194  
Universidad de Santiago de Chile  
Santiago, Chile

Available in: <http://www.redalyc.org/articulo.oa?id=85611774003>

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## Recent advances in the use of *Panax ginseng* as an analgesic: a systematic review

[Recientes avances del uso del *Panax ginseng* como analgésico: una revisión sistemática]

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### Abstract

Ginseng is a widespread herbal medicine that has been used in China, Korea and Japan for thousands of years. Ginsenosides or ginseng saponins are the active principles of *Panax ginseng*. Ginseng is widely used as a general tonic and adaptogen; however, experimental and clinical studies have shown it to have beneficial effects on a wide range of pathological conditions including cardiovascular diseases, cancer, immune deficiency and neurodegenerative disorders. Recent studies have also suggested that some of the active ingredients of ginseng may exert a beneficial effect on nociception. This review focuses on the recent scientific evidence of the reported medicinal effects of ginseng with particular emphasis on its analgesic-like effects.

**Keywords:** *Ginseng extract; Ginsenoside; Antinociception; Analgesia.*

### Resumen

El ginseng es una hierba medicinal que está difundida en todo el mundo. Países como China, Corea y Japón la han utilizado por muchos siglos. Los ginsenosidos o saponinas de ginseng son los principios activos del *Panax ginseng*. Este es ampliamente utilizado como un tónico y adaptógeno; sin embargo, algunos estudios experimentales y clínicos han demostrado efectos beneficiosos en gran variedad de condiciones patológicas como enfermedades cardiovasculares, cáncer, deficiencia inmune y desórdenes neurodegenerativos. Recientes estudios sugieren que algunos de los componentes activos del ginseng pueden ejercer un efecto beneficioso en la nocicepción. Esta revisión se centra en la evidencia científica más reciente de los efectos medicinales anteriormente citados del ginseng, con especial énfasis en sus efectos analgésicos.

**Palabras Clave:** *Extracto de ginseng, Ginsenosidos, Antinocicepción, Analgesia.*

**Recibido | Received:** February 2, 2009.

**Aceptado en Versión Corregida | Accepted in Corrected Version:** April 10, 2009.

**Publicado en Línea | Published Online:** April 13, 2009.

**Declaración de Intereses | Declaration of interests:** Authors have no competing interests

**Financiación | Funding:** none stated.

**This article must be cited as:** Alessandra de Sousa Braz, Margareth de Fátima F. Melo Diniz, Reinaldo Nóbrega de Almeida. 2009. Recent advances in the use of *Panax ginseng* as an analgesic: a systematic review. Bol Latinoam Caribe Plant Med Aromat 8(3):188 – 194. {EPub April 13, 2009}.

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## INTRODUCTION

For hundreds of years, traditional Chinese, Korean and Japanese medicine has used medicinal herbs such as ginseng as an essential therapy for weakness and fatigue. Ginseng is derived from the roots of several species of plants (Kiefer and Pantuso, 2003). The types of ginseng most frequently used are Asian or Korean ginseng (*Panax ginseng* C.A. Meyer), American ginseng (*Panax quinquefolius* C.A. Meyer) and Japanese ginseng (*Panax japonicus* C.A. Meyer) (Yuan and Dey, 2001; Coleman et al., 2003). The genus *Panax* (Araliaceae) is comprised of around 11 slow-growing species (perennial plants with strong roots) that grow in the northern hemisphere, typically in the cold climates of eastern Asia, particularly northern Korea and eastern Siberia and Russia. The Table 1 summarizes the scientific classification of the *Panax* genus (Winston and Maimes, 2007).

Ginseng is used in several ethnomedical systems as an adaptogen. However, other species endowed with similar adaptogenic effects are popularly also known as gingseng. These include -among others- *Eleutherococcus senticosus* (Siberian ginseng), *Pseudostellaria heterophylla* (Prince ginseng), *Withania somnifera* (Indian ginseng) and *Pfaffia paniculata* (Brazilian ginseng) (Davydov and Krikorian, 2000; Radad et al., 2006).

The chemical composition of the different *Panax* species is relatively similar; however, in general each species exerts a specific effect on the body (Vuksan et al., 2000; Radad et al., 2006). The principal active components of ginseng are the ginsenosides or ginseng triterpenoid saponins. Approximately 38 types of ginsenosides have been identified (Rhim et al., 2002; Leung et al., 2007; Choi et al., 2008), which account for the pharmacological effects of these plants in the modulation of angiogenesis, for their popular adaptogenic properties and their effects on the central nervous system (CNS). The concentration of each ginsenoside varies depending on the species of *Panax*, the time of the year, the time it takes to be collected, the part of the plant and the methods of preservation or extraction used. Some studies have indicated steroid hormone receptors as possible molecular targets of ginseng, which may explain the diverse cellular and physiologic effects of this plant (Rege et al., 1999; Yuan and Dey, 2001; Coleman et al., 2003; Leung et al., 2007).

According to Attele et al. (1999), some of the pharmacological effects of ginsenosides may be

explained by their capacity to target multiple receptors at the plasma membrane as well as by their ability to cross the membrane freely and induce effects by acting directly on the nucleus. However, in many cases, the mechanisms of action of the ginsenosides remain unknown.

**Table 1.** Scientific classification of the *Panax* genus.

Kingdom	<i>Plantae</i>
Division	<i>Magnoliophyta</i>
Class	<i>Magnoliopsida</i>
Order	<i>Apiales</i>
Family	<i>Araliaceae</i>
Subfamily	<i>Aralioideae</i>
Genus	<i>Panax</i>
Main species	<i>Panax notoginseng</i> (San Qi) <i>Panax bipinnatifidus</i> (Seem.) <i>Panax ginseng</i> (C.A. Meyer) <i>Panax japonicus</i> (C.A. Meyer) <i>Panax quinquefolium</i> (C.A. Meyer) <i>Panax vietnamensis</i> (Ha eand Grushv) <i>Panax wangianum</i> (Suu) <i>Panax zingiberensis</i> (Wu and Feng.) <i>Panax pseudoginseng</i> (Wall) <i>Panax stipuleanatus</i> (Tsai and Feng.) <i>Panax trifolium</i> L.

The basic chemical structure of all ginsenosides is similar, consisting of a gonane steroid nucleus with 17 carbon atoms arranged in four rings. The characteristic biological responses for each ginsenoside are attributed to the differences in the type, position, and number of sugar moieties attached by the glycoside bond at C-3 and C-6. Based on their structural differences, they can be classified into three categories: the panaxadiol group (Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1), the panaxatriol group (Re, Rf, Rg1, Rg2, Rh1), and the oleanolic acid group (Ro) (Radad et al., 2006).

This review focuses on the recently reported medicinal effects of ginseng and summarizes the current body of evidence supporting the use of ginseng particularly with respect to its antinociceptive / analgesic properties.

### General use of *Panax ginseng*

Based on experimental studies, an effect of some types of ginseng on the central nervous system (CNS) has been suggested, particularly in neurodegenerative disorders such as senile dementia and Parkinson's disease. Following the rapid exposure of cortical cell culture to glutamate, an excitatory neurohormone of

the CNS, significant neuronal death occurred. This damage was significantly reduced when the cell cultures were pretreated with the Rb1 and Rg3 ginsenosides, resulting in inhibition of the overproduction of nitric oxide, which is routinely followed by neurotoxicity. In glutamate-treated cells, these ginsenosides inhibited the formation of malondialdehyde and reduced calcium influx, suggesting a significant neuroprotective effect (Kim et al., 1998).

It has been suggested that Rg3 ginsenoside inhibits both N-methyl-D-aspartate (NMDA) and non-NMDA glutamate receptors, which contribute significantly to many neurological disorders particularly brain ischemia, trauma, stroke, and seizures (Radad et al., 2006).

The neuroprotective effect of the Rb1 and Rg1 ginsenosides (extracted from ginseng roots) has been demonstrated *in vitro* in spinal cord neurons. These ginsenosides were found to protect the spinal neurons from the excitotoxicity induced by glutamate and kainic acid, as well as from the oxidative stress induced by H<sub>2</sub>O<sub>2</sub>, in a dose-dependent manner (20-40 micro M), thereby reinforcing the need for more studies on its therapeutic use in spinal cord injuries (Liao et al., 2002).

It has also been shown to have an effect on the immune system by enhancing phagocytosis, the activity of natural killer cells and interferon production (Kiefer and Pantuso, 2003), and has beneficial effects as an antioxidant (Hofseth and Wargovich, 2007). Kim et al., 2007, found that transgenic *P. ginseng* inhibited the production of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, IL-8, and the expression of cyclooxygenase-2 in phorbol 12-myristate 13-acetate (PMA) plus calcium ionophore A23187 (PMACI)-stimulated human mast cells (HMC-1). Additionally, they have shown that transgenic *P. ginseng* suppressed the intracellular calcium level induced by PMACI. These results provide new insights into the pharmacological actions of transgenic *P. ginseng* as a potential molecule for use in therapy in mast cell-mediated inflammatory diseases (Kim et al., 2007).

Studies carried out *in vivo* have shown the beneficial effects of *P. ginseng* in a wide range of pathological conditions such as diabetes mellitus (Suzuki and Hikino, 1989), cardiovascular diseases (Buettner et al., 2006) cancer (Panwar, 2005; Mannaa et al., 2006), inflammatory processes (Li and Chu, 1997; Park et al., 2005; Raddad et al., 2006) and in animal models of behavioral disorders (Einat, 2007).

### Clinical use of *Panax ginseng*

In clinical studies, ginseng led to an improvement in climacteric symptoms, particularly fatigue, insomnia and depression, in postmenopausal women (Tode et al., 1999). In addition, a positive effect has been shown on the immune system (Kaneko and Nakanishi, 2004) in the control of arterial hypertension and on cardiovascular function (Zhou et al., 2004), in the treatment of psychological abnormalities and in conditions associated with diabetes mellitus (Buettner et al., 2006). It has also been found to reduce the occurrence of viral respiratory infections in the elderly when compared to a placebo group (McElhaney et al., 2004).

Nevertheless, controversial results have been published in the literature with respect to the use of ginseng for the treatment of psychological abnormalities and only a modest effect has been reported with respect to its hypoglycemic activity (Kiefer and Pantuso, 2003). Ginseng has been reported to have a positive effect in the treatment of herpes simplex virus type II infection, the common cold, ethanol-induced gastric lesions and aspirin-induced gastric ulcers (Kaneko and Nakanishi, 2004).

Used primarily as a general tonic and to restore homeostasis, and despite reports of improvements in psychomotor performance in healthy volunteers (D'Angelo et al., 1986), there are contradictory reports in the literature (Coleman et al., 2003; Kiefer and Pantuso, 2003).

The use of ginseng was found to result in an improvement in the quality of life of patients with chronic renal failure and an improvement in mental and psychosocial health following four weeks of treatment; however, these effects tended to attenuate with prolonged use (Ellis and Reddy, 2002). In 2003, Coleman et al. analyzed studies carried out on the effects of this plant on quality of life and found that, although the majority of studies failed to find any significant differences associated with the use of ginseng in the final scores, the possibility that an improvement in some of the parameters of quality of life was indeed related to its use could not be discarded.

The efficacy of ginseng as a therapeutic option for the treatment of male erectile dysfunction (Hong et al., 2002), and the improvement in the survival of patients with advanced stomach cancer during postoperative chemotherapy (Suh et al., 2002) have been demonstrated in double-blind clinical trials.

### ***Panax ginseng* and analgesia: possible molecular mechanisms**

Several studies have demonstrated the antinociceptive effects of ginseng extract in experimental models *in vitro* (Nah and McCleskey, 1994; Hahn et al., 2000; Sampson et al., 2000) and *in vivo* (Ramarao and Bhargava, 1990; Mogil et al., 1998; Yoon et al., 1998; Shin et al., 1999; Nah et al., 2000; Suh et al., 2000; Choi et al., 2003; Nemmani and Ramarao, 2003).

Studies using the whole-cell and inside-out configurations of the patch-clamp technique showed that the total saponins of ginseng (ginsenosides), when applied at the dose of 100 µg/mL concomitantly with capsaicin (1 µg/mL), directly blocked the capsaicin-activated calcium channels, resulting in attenuation of the currents of these ions in sensorial neurons of rats (Hahn et al., 2000).

The Rg3 ginsenoside was also able to inhibit calcium channels in the rat dorsal root ganglion neurons. Studies using the patch-clamp technique found that the application of the entire extract of ginseng suppressed calcium channel currents in a dose-dependent manner. The experimental use of selective blockers showed that the ginseng saponins are able to modulate the currents in the L, N and P calcium channels, suggesting that part of the pharmacological basis of the antinociceptive effect of ginseng, particularly the Rg3 ginsenoside, involves modulation of the calcium channels (Rhim et al., 2002).

Voltage-gated Na<sup>+</sup> channels in primary sensory neurons play important roles in pain perception. The effects of a polyacetylenic compound, (9R,10S)-epoxyheptadecan-4,6-diyne-3-one (EHD), isolated from ginseng extract, were investigated in tetrodotoxin-sensitive (TTX-S) and tetrodotoxin-resistant (TTX-R) Na<sup>+</sup> currents in acutely dissociated rat dorsal root ganglion neurons. In this study, EHD inhibited both Na<sup>+</sup> currents in a concentration-dependent manner, accelerated the inactivation of both Na<sup>+</sup> currents and produced a hyperpolarizing shift of the steady-state inactivation curve. In addition, EHD suppressed the maximal Na<sup>+</sup> current at negative holding potentials at which the channels are relieved from inactivation. Thus, EHD appears to bind both resting and inactivated channels. According to these authors, EHD, a polyacetylene derived from ginseng, by inhibiting Na<sup>+</sup> currents in primary sensory neurons, may contribute to the analgesic effect of ginseng (Choi et al., 2008).

*In vivo* studies, the effects of the administration of ginseng extract on nociception and colonic temperature in Sprague-Dawley rats, and the possible involvement of opioid receptors in its pharmacological activities were evaluated by Ramarao and Bhargava in 1990. Following intraperitoneal administration of the extract at doses of 25, 50, 100 and 200 mg/kg, either alone or in combination with morphine (8 mg/kg), ginseng was found to induce analgesia and hypothermia at high doses (100 and 200 mg/kg) through a non-opioid mechanism, since these effects were not antagonized by naloxone. Since ginseng was able to induce analgesia, its interaction with morphine was investigated and results showed that when the extract was administered together with morphine, the acute pharmacological effects evoked by morphine in rats, such as analgesia and hyperthermia at a dose of 8 mg/kg, and catalepsy at a dose of 50 mg/kg were antagonized by ginseng in a dose-dependent manner. In other words, to antagonize the analgesic effect of morphine, only intermediate doses (25 to 50 mg/kg) were effective.

Next, it was found that, like opioid analgesics, the Rf ginsenoside inhibited calcium channels in primary sensorial neurons using an unidentified receptor bound to the G protein, unlike the alpha-2 adrenergic receptors, gamma-amino butyric acid type B (GABA<sub>B</sub>), muscarinic or opioid receptors (Nah and McCleskey, 1994).

Since inhibition of the calcium channels in sensorial neurons contributes towards antinociception by the opioids, Mogil et al. (1998) tested the analgesic effects of the Rf ginsenoside in experimental models of acute and chronic pain, and reported a dose-dependent, antinociceptive effect in the models used to evaluate chronic pain. This effect was accompanied by inhibition of the calcium channels in the large nociceptors. Additionally, the authors reported an antinociceptive effect with the use of the raw, unprocessed extract of ginseng, suggesting that Rf was not the only component of the extract that participated actively in the antinociceptive effect.

The effects of ginsenosides on the nociceptive response to intrathecally-administered substance P (SP) were also investigated in mice. Using this route of administration, both pretreatment and concomitant treatment with ginsenosides inhibited the SP-induced nociceptive responses (scratching, biting or licking the distal portion of the paw) in a dose-dependent manner. In this study, Yoon et al. (1998) reported that ginsenosides showed antinociceptive activity in the

formalin test and that this effect was due to substance P-mediated blockade of the postsynaptic nociceptive information at spinal level. Choi et al. (2003) obtained similar results with Rb2, Rc, Rd and R2 ginsenosides injected supraspinally and Rb1, Rb2, Rd and Rf ginsenosides administered into the spinal cord.

Following confirmation that ginsenosides were effective in inhibiting SP-induced nociceptive responses, Nah et al. (2000) demonstrated their central activity following inhibition of the pain induced experimentally by an injection of capsaicin into the hind paw of the animal. These investigators reported that the plant inhibited pain in a dose-dependent manner only when administered intrathecally or intracerebroventricularly, while this effect was not found when the ginsenoside was applied subcutaneously to the plantar surface prior to the injection of capsaicin. As in the study carried out by Shin et al. (1999) with Rc, Rd and Re ginsenosides in models of chronic pain in which significant responses related to the noxious chemical stimulus were obtained, pretreatment with naloxone failed to block the antinociceptive effect of the intrathecal administration of the ginsenoside, suggesting that the latter exerts central antinociceptive effects in the spine and/or supraspinal region but not in peripheral nociceptors. Moreover, these investigators found that their effects were not mediated by the opioid receptors (Shin et al., 1999; Nah et al., 2000).

Rb1, Rb2, Rc, Rd and Rg1 ginsenosides blocked the antinociceptive effect induced by a kappa-opioid agonist (U50,488H) when administered into the spinal cord and in the supraspinal region of mice, and the same response was obtained by Rb2 and Re ginsenosides administered into the supraspinal region (Suh et al., 2000).

Interference by the Rf ginsenoside in the analgesic effect induced by the opioid agonist U50,488 H was reported by Nemmani and Ramarao in 2003 using the tail-flick test in mice. Intraperitoneal administration of 40 mg/kg of the agonist produced analgesia, and the inhibition of tolerance of the agonist to analgesia by Rf remained unaffected by flumazenil (0.1 mg/kg), a benzodiazepine receptor antagonist, and by picrotoxin (1 mg/kg), a chloride channel blocker in the GABAA receptor. The results showed that Rf potentiated U-50,488H-induced analgesia and inhibited its tolerance to analgesia, suggesting that the effect of Rf on U50,488H, in mice occurs through a non-opioid path insensitive to the calcium channels, sensitive to dihydropyridine and not GABAergic.

Clinical studies with analgesic activities of *P. ginseng* on literature are insufficient. Others saponins were studied. To evaluate the therapeutic effect and possible mechanism of total *Panax notoginseng* saponins (PNS) for treatment of rheumatoid arthritis (RA), and to observe its safety and influence on RA immune related inner environment, 84 patients were randomly assigned to two groups. All were treated with the routine therapy with diclofenac sodium, Leflunomide and prednisone, but for the 43 patients in the treatment group PNS was given additionally. Significant improvement of clinical symptoms and change of indexes including platelet counts, immunoglobulins (IgG, IgA, IgM), complement (C3), rheumatoid factor (RF), C-reactive protein (CRP), ceruloplasmin (CER), haptoglobin (HPT), and alpha1-acid glycoprotein (AAG) were observed in both groups after treatment, and the effect in the treatment group was better ( $P < 0.05$  or  $P < 0.01$ ). PNS can significantly improve the condition of patients enhance the therapeutic effect in treating RA, through regulating the disordered immunity and improving the effect of anti-inflammatory and analgesia (Zhang et al, 2007).

## CONCLUSION

In experimental models, the antinociceptive/analgesic effects of ginseng extract, particularly the effect of ginsenosides on inhibition of substance P-induced nociceptive response and the inhibition of calcium channels in the sensorial spinal and or supraspinal neurons of rats, suggest that ginseng has a potential analgesic effect and a central antinociceptive effect; rather than on the peripheral nociceptors. Clinical studies with analgesic activities of *P. ginseng* on literature are scarce. Therefore, in view of the positive findings of clinical trials performed with appropriate methodology, the medicinal and analgesic effects of ginseng extract may represent an option for the treatment of acute and/or chronic pain, particularly since the costs involved in marketing this substance appear to be accessible.

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