



## Mini-review article

## Ginsenoside Rd and ischemic stroke; a short review of literatures



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## ABSTRACT

*Panax ginseng* is a well-known economic medical plant that is widely used in Chinese traditional medicine. This species contains a unique class of natural products—ginsenosides. Recent clinical and experimental studies have presented numerous lines of evidence on the promising role of ginsenosides on different diseases including neurodegenerative diseases, cardiovascular diseases, and certain types of cancer. Nowadays, most of the attention has focused on ginsenoside Rd as a neuroprotective agent to attenuate ischemic stroke damages. Some of the evidence showed that ginsenoside Rd ameliorates ischemic stroke-induced damages through the suppression of oxidative stress and inflammation. Ginsenoside Rd can prolong neural cells' survival through the upregulation of the endogenous antioxidant system, phosphoinositide-3-kinase/AKT and extracellular signal-regulated protein kinase 1/2 pathways, preservation of mitochondrial membrane potential, suppression of the nuclear factor-kappa B, transient receptor potential melastatin, acid sensing ion channels 1a, poly(ADP-ribose) polymerase-1, protein tyrosine kinase activation, as well as reduction of cytochrome c-releasing and apoptosis-inducing factor. In the current work, we review the available reports on the promising role of ginsenoside Rd on ischemic stroke. We also discuss its chemistry, source, and the molecular mechanism underlying this effect.

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## 1. Introduction

Stroke, which statistically ranks as the third leading cause of death and as the most important cause of permanent disability worldwide, is classified into ischemic and hemorrhagic stroke [1–3]. Nearly 80% of stroke patients suffer from ischemic stroke, which results from artery and/or vascular occlusion inducing a transient or permanent reduction in blood supply to the different regions of the brain [4,5]. Old age, smoking, and concomitant diseases such as obesity, diabetes, and hypertension are risk factors of stroke [6–10]. Statistical data also show that the occurrence of stroke events is asymmetrical in different sexes and ethnicities [11,12].

In addition, stroke is associated with several complications including depression, insomnia, or cognitive impairment, which have detrimental effects on therapeutic outcomes, increasing

medical costs and mortality rate [13–16]. Experimental and clinical evidence also showed that depending on the ischemic/reperfusion duration, infarct volume and site, patient age, and the presence of concomitant diseases, the stroke-induced complications and mortality rate are different [14,17–20]. Oxidative stress and systemic inflammation appear to have a key role in the pathophysiology of ischemic stroke and stroke-induced complications [21–23]. A growing body of evidence obtained from epidemiological studies shows that diets containing large amounts of vegetables and fruits decrease the risk of ischemic stroke [24–26]. This reality is supported by extensive experimental studies on isolated phytochemicals [27–30]. A plethora of evidence also shows the antioxidant and anti-inflammatory effects of these phytochemicals [31–34], which seem to be promising compounds against ischemic stroke [35,36]. During the past decades, much attention has been paid to health promotion related to the activity of phytochemicals and a

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great revolution occurred in the use of medical plant-derived phytochemicals as effective strategy for the treatment of different diseases [37–45].

*Panax ginseng* Meyer (Korean red ginseng) is a well-known medicinal plant from eastern Asian countries, especially Korea, China, and Japan [46,47], and its root has been used since ancient times for the treatment of numerous diseases and increasing physical strength [48,49]. The word *Panax* originates from the word “panacea,” which means “cure all diseases,” and refers to a traditional belief about its promising effects on longevity and health promotion [46]. The therapeutic role of *Panax ginseng* on several diseases such as cancer and cardiovascular diseases, has been reported by recent experimental and clinical studies on ginseng and/or its bioactive constituents [50–54]. The first attempts to isolate the active constituents of ginseng began many years ago, leading to the isolation of ginsenosides in 1963 [55]. To date, > 40 different ginsenosides have been found [56]. Extensive studies evaluated the different pharmacological activities of ginsenosides, such as their ability to suppress inflammation and oxidative stress as well as their vasorelaxation effect [57–61]. Many lines of evidence also showed the promising effects of ginseng and its purified ginsenoside constituents on cardiovascular disease and its risk factors [54,62–68]. The promising role of ginsenosides Rd on ischemic stroke is widely publicized [69–71]. The aim of this paper is to review the available reports on the therapeutic role of ginsenosides Rd on ischemic stroke. We also discuss the molecular mechanism underlying this effect, as well as the chemistry and safety of ginsenoside Rd.

## 2. Source and chemistry

Ginseng has been used for thousands of years in folk medicine in Eastern Asia. The most popular ginseng comes from the root of *P. ginseng* Meyer, a slow-growing perennial plant belonging to the family Araliaceae. The plant is native to China and Korea but is now widely cultivated in other countries including Japan, Russia, United States, and Canada. The vast array of medicinal uses of *P. ginseng* includes its use as a remedy against aging, diabetes, sleep disorders, and sexual dysfunction [72,73]. In addition to ginseng from *P. ginseng*—commonly known as Asian, Chinese, or Korean ginseng—American ginseng (from *Panax quinquefolius*) is also available.

The active principles responsible for the pharmacological activities of ginseng are a group of unique triterpene glycosides or saponins called ginsenosides. The chemical structure of one of the best-known active ingredients, ginseng Rd, along with some related ginsenosides, is shown in Fig. 1. These compounds are based on the dammarane triterpene skeleton that is hydroxylated at three positions (C-3, C-12, and C-20 positions) to produce protopanaxadiol (Fig. 1). Based on the variability in the type of sugars and the degree of glycosylation at the C-3 and C-20 positions, several ginsenosides of protopanaxadiol skeleton have been identified from ginseng (Fig. 1). Remarkably, hydroxylation at the C-6 position of protopanaxadiol is also possible, leading to further structural diversities via glycosylation.

Today, the quality control of ginseng is a difficult task owing to the diversity of plant sources, which include *P. ginseng*, *Panax notoginseng*, *P. quinquefolius*, and *Panax japonicas*, and the variability in the composition (> 150 ginsenosides are known in the genus, and > 35 are found in the roots) [56,62,74] based on plant age, harvesting conditions, and growing media such as soil, temperature, light intensity, and water content [75–79]. One alternative approach is to use the most active ginsenoside, such as ginsenoside Rd; however, the low yield (as low as 0.4%) coupled with the difficulty and high cost of isolating the compound from the

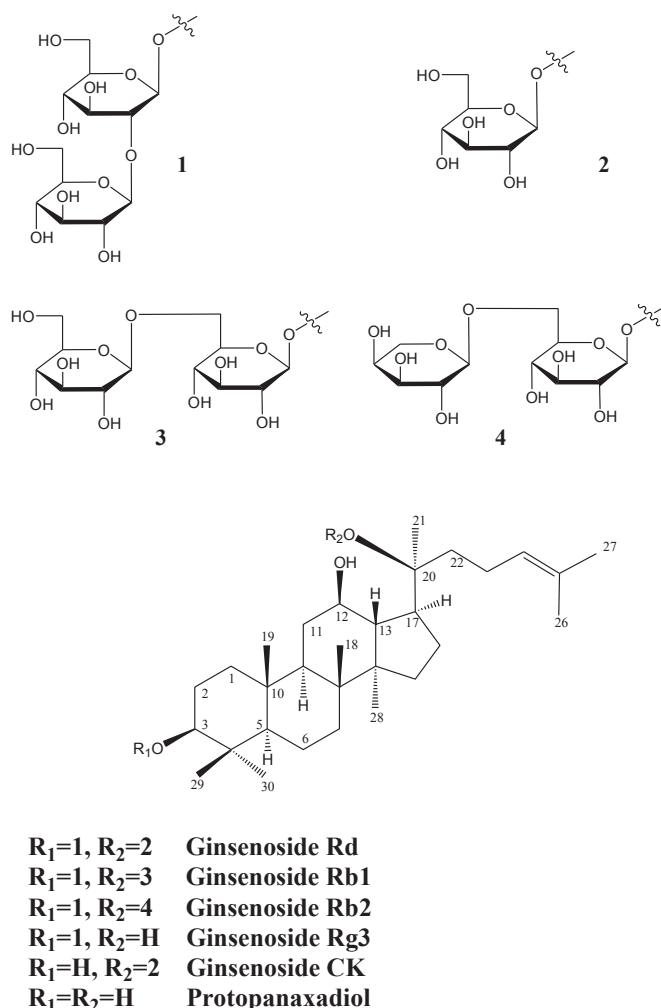
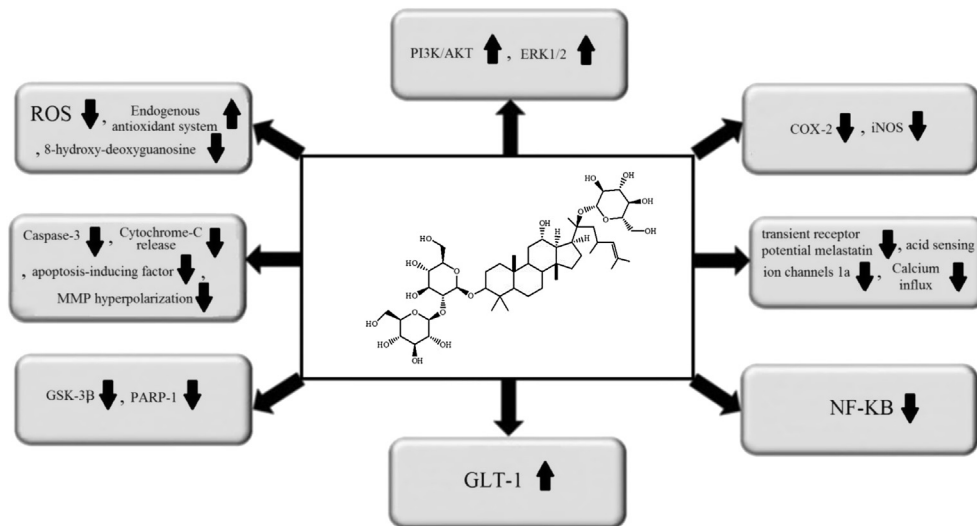


Fig. 1. Structure of ginsenoside Rd and related ginsenosides.

complex mixture pose a great barrier. Fortunately, the major component of ginsenosides is Rb1, which differs from Rd in that it has two glucose units at C-20 position instead of only one (Fig. 1). To date, a number of enzyme and/or microbial-based biotransformation [80–88] methodologies have been proposed to obtain ginsenoside Rd. The exploitation of ginsenosides from plant cell cultures is also an active topic of current research [89,90]. Further developments in these research areas are therefore likely to make the concept of using ginsenoside Rd as a single chemical entity very feasible.

## 3. Ginsenoside Rd and ischemic stroke

The promising effect of pre- and/or posttreatment of ginsenoside Rd on ischemic stroke-induced neural damages has been studied in different experimental models including transient middle cerebral artery occlusion (tMCAO) in rat and mice [91–93], oxygen glucose deprivation-induced damages to hippocampal neuron [70], or glutamate-induced damages in rat cortical neurons [94]. Evidence obtained from *in vitro* and *in vivo* studies shows that ginsenoside Rd treatment prior to and/or following an ischemic stroke can reduce infarct volume [69,91,92], increase neuronal survival (Fig. 2) [70,94–96], and enhance cognitive and neurological functions [91,92,97]. Ginsenoside Rd administration to a Sprague–Dawley rat has been shown to downregulate ischemic stroke-



**Fig. 2.** Molecular mechanisms underlying the promising effects of ginsenoside Rd on ischemic stroke. COX-2, cyclooxygenase-2; ERK  $1/2$ , extracellular signal-regulated protein kinases 1 and 2; GLT-1, glial glutamate transporter-1; GSK-3 $\beta$ , glycogen synthase kinase-3 $\beta$ ; iNOS, inducible nitric oxide synthase; MMP, mitochondrial membrane potential; NF- $\kappa$ B, nuclear factor-kappa B; PARP-1, poly(ADP-ribose) polymerase 1; PI3K/AKT, phosphatidylinositol 3-kinase/AKT; ROS, reactive oxygen species.

induced tau protein phosphorylation at Ser199/202 and PHF-1 sites through the downregulation of glycogen synthase kinase-3 $\beta$  and to enhance ischemia-induced cognitive impairment [97]. Ginsenoside Rd administration has also been shown to upregulate the protein kinase B/AKT pathway and, from this, suppress glycogen synthase kinase-3 $\beta$  activity [97]. Ginsenoside Rd administration after tMCAO upregulates glial glutamate transporter-1 (GLT-1) expression and promotes glutamate clearance in rats [95]. Similarly, exposing ginsenoside Rd to astrocyte cells increases glutamate uptake after oxygen-glucose deprivation. It is also reported that phosphorylated protein kinase B and phospho-extracellular signal-regulated protein kinase (ERK) 1/2 pathways have a crucial role in the promising effect of ginsenoside Rd on glutamate uptake and GLT-1 expression [95]. Ginsenoside Rd is also a selective and competitive Ca<sup>2+</sup> receptor antagonist and, therefore, can suppress calcium influx after cytotoxic injuries [93]. A previous study showed that pretreatment with ginsenoside Rd (10 mg/kg) increases acid sensing ion channels 2a and suppresses transient receptor potential melastatin, and acid sensing ion channels 1a expression in tMCAO-induced ischemic rats and, through this effect, prolongs neuronal survival [93]. An *in vitro* study on rat cortical neurons reported that ginsenoside Rd administration dose-dependently suppresses glutamate-induced DNA laddering and apoptosis through the suppression of glutamate-induced caspase-3 activation and Ca<sup>2+</sup> entry [94]. Another study showed that pretreatment with ginsenoside Rd (10 mg/kg) inhibits poly(ADP-ribose) polymerase-1 and consequently downregulates apoptosis-inducing factor translocation and nuclear factor-kappa B p65 subunit nuclear accumulation in Dawley rats suffering from right middle cerebral artery occlusion [96]. This finding supported the concept that both the antiapoptotic and anti-inflammatory effects of ginsenoside Rd may be responsible for its promising effects on ischemic stroke [96].

Another study on 16- to 18-month-old mice suffering from tMCAO-induced ischemic stroke shows that pretreatment with ginsenoside Rd (10–50 mg/kg) significantly decreases cortical and striatal infarct size and oxidative stress (DNA damage, protein carbonyl formation, and lipid peroxidation) [91]. Ginsenoside Rd also upregulates the endogenous antioxidant system, sustains the mitochondrial respiratory chain complex and aconitase activities, downregulates mitochondrial hydrogen peroxide leakage,

and stabilizes mitochondrial membrane potential [91]. In addition to these effects, another similar report also showed that ginsenoside Rd administration (50 mg/kg) to rats prior to tMCAO significantly decreases the infarcted area (52.8%), and decreases the lactate/pyruvate ratio, the reactive oxygen species production, cytochrome releasing, and apoptosis-inducing factor [92]. Similarly, an *in vitro* study showed that exposure to ginsenoside Rd can also protect mitochondria against calcium-induced damages through downregulation of reactive oxygen species generation, suppression of mitochondrial membrane potential hyperpolarization, and amelioration of mitochondrial swelling [92]. In another *in vitro* study, a 2-hour oxygen-glucose deprivation followed by a 24-hour reoxygenation in cultured hippocampal neurons showed that ginsenoside Rd administration upregulates the endogenous antioxidant system including glutathione and antioxidant enzymes, suppresses reactive oxygen species production and lipid peroxidation, preserves mitochondrial membrane potential, and eventually, decreases apoptotic death [70]. The treatment with ginsenoside Rd at doses of 10–50 mg/kg decreases the infarct size and enhances neurological function in both tMCAO-induced ischemic mice and rats [69,91]. Ginsenoside Rd also upregulates the endogenous antioxidant system in ischemic penumbra, and decreases 8-hydroxy-deoxyguanosine (marker of DNA damage), hydroxyl radicals formation, protein carbonyl, malondialdehyde, and 4-hydroxynonenal (markers of lipid peroxidation), as well as advanced glycosylation end product levels [69]. It also decreases inflammation through the downregulation of inducible nitric oxide synthase, cyclooxygenase-2, and microglial activation [69].

A randomized, double-blind, placebo-controlled, Phase II multicenter trial study on 199 patients suffering from ischemic stroke showed that ginsenoside Rd infusion at doses of 10 and 20 mg/kg for 2 weeks significantly enhanced the National Institutes of Health Stroke Scale when compared with the placebo group [98]. However, ginsenoside Rd does not improve stroke disability and daily activity in Barthel index and the modified Rankin scales [98]. The authors of the study concluded that ginsenoside Rd may be beneficial for ischemic patients [98]. Another randomized, double-blind, placebo-controlled, multicenter trial study on 390 patients suffering from acute ischemic stroke,

showed that a 2-week intravenous infusion of ginsenoside Rd significantly enhanced the primary outcome and improved the National Institutes of Health Stroke Scale and modified Rankin scale at 90 days [71]. The study suggested that ginsenoside Rd can have a promising neuroprotective role as adjuvant therapy in acute ischemic patients.

#### 4. Conclusion and recommendation

In conclusion, the available data suggest that the antiapoptotic, antioxidant, and anti-inflammatory activities of ginsenoside Rd as well as its ability to suppress calcium influx, may play a key role in the neuroprotective action of this compound against ischemic stroke. Ginsenoside Rd's ability to upregulate GLT-1, phosphatidylinositol 3-kinase/AKT, and ERK1/2 signaling pathways, and to inhibit poly(ADP-ribose) polymerase 1, glycogen synthase kinase-3 $\beta$ , nuclear factor kappa B, apoptosis-inducing factor, cytochrome c release, and caspase activation plays crucial role in prolonging neuronal cell survival during an ischemic stroke and in the recovery of cognitive function. However, owing to the lack of clinical studies on ginsenoside Rd, it is difficult to make a clear decision. We recommend that future studies on ginsenoside Rd should focus on the following areas: (1) molecular mechanisms underlying the beneficial role of ginsenoside Rd on ischemic stroke; (2) pharmacokinetic studies on ginsenoside Rd and finding methods to increase its bioavailability using different delivery systems; (3) pharmacodynamic studies on ginsenoside Rd and its possible interaction with well-known ischemic stroke drugs; and (5) clinical studies to ascertain the best effective doses.

#### Conflicts of interest

There is no conflict of interest.

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