J Ginseng Res 39 (2015) 299–303

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Mini-review article

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

Seyed Fazel Nabavi [1], Antoni Sureda [2], Solomon Habtemariam [3], Seyed Mohammad Nabavi [1,*]

[1] Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Research Group on Community Nutrition and Oxidative Stress, University of Balearic Islands, and CIBERobn (Physiopathology of Obesity and Nutrition), Palma de Mallorca, Balearic Islands, Spain
[3] Pharmacognosy Research Laboratories, Medway School of Science, University of Greenwich, Chatham-Maritime, Kent ME4 4TB, UK

ARTICLE INFO

*Article history:*
Received 18 December 2014
Accepted 8 February 2015
Available online 23 February 2015

*Keywords:*
ginsenoside Rd
*Panax ginseng*
signal transduction

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.


## 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

* Corresponding author. Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, P.O. Box 19395-5487, Tehran, Iran. Tel.: +98 21 88617712; fax: +98 21 88617712.
*E-mail address:* Nabavi208@gmail.com (S.M. Nabavi).

p1226-8453 e2093-4947/$ – see front matter 
http://dx.doi.org/10.1016/j.jgr.2015.02.002

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 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.

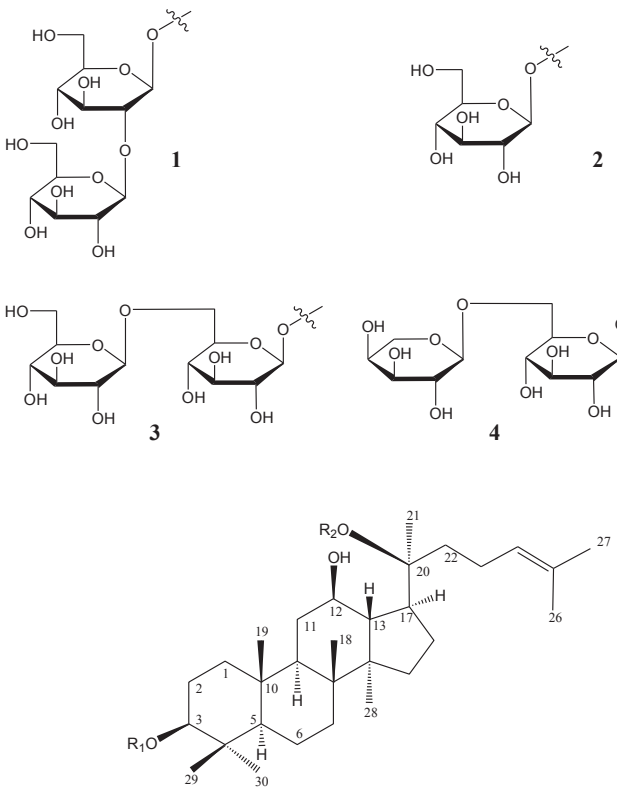


**Fig. 1.** Structure of ginsenoside Rd and related ginsenosides.

## 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-

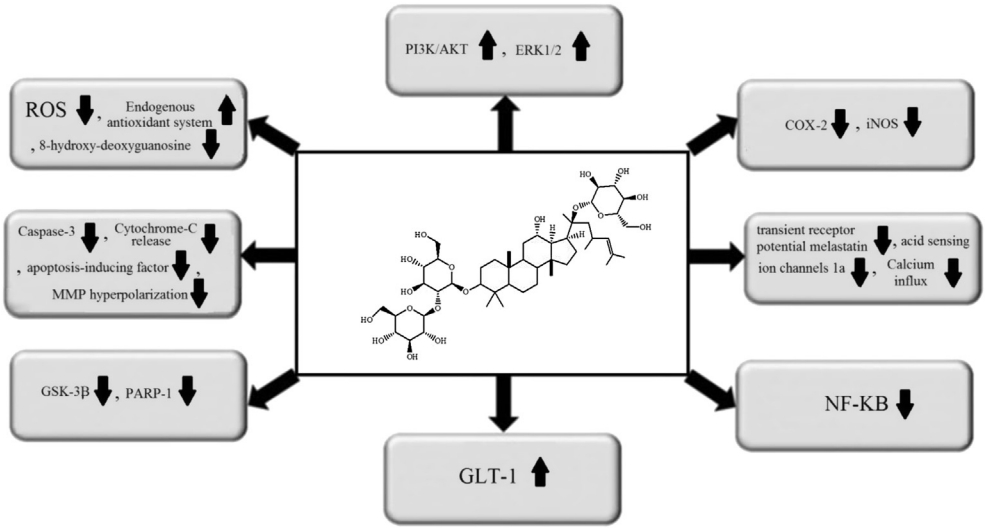


**Fig. 2.** Molecular mechanisms underlying the promising effects of ginsenoside Rd on ischemic stroke. COX-2, cyclooxygenase-2; ERK $^{1}/_{2}$ , extracellular signal-regulated protein kinases 1 and 2; GLT-1, glial glutamate transporter-1; GSK-3β, glycogen synthase kinase-3β; iNOS, inducible nitric oxide synthase; MMP, mitochondrial membrane potential; NF-κB, 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-3β 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-3β 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 $Ca^{2+}$ 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 $Ca^{2+}$ 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-3β, 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.

## References


[1] Mukherjee D, Patil CG. Epidemiology and the global burden of stroke. World Neurosurg 2011;76:S85–90.
[2] Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. Neurol Clin 2008;26:871–95.
[3] Kleinig TJ, Vink R. Suppression of inflammation in ischemic and hemorrhagic stroke: therapeutic options. Curr Opin Neurol 2009;22:294–301.
[4] Nabavi SF, Li H, Daglia M, Nabavi SM. Resveratrol and stroke: from chemistry to medicine. Curr Neurovasc Res 2014;11:390–7.
[5] Hossmann K-A. The two pathophysiologies of focal brain ischemia: implications for translational stroke research. J Cereb Blood Flow Metab 2012;32:1310–6.
[6] Bonita R. Epidemiology of stroke. Lancet 1992;339:342–4.
[7] Schwartz SW, Carlucci C, Chambless LE, Rosamond WD. Synergism between smoking and vital exhaustion in the risk of ischemic stroke: evidence from the ARIC study. Ann Epidemiol 2004;14:416–24.
[8] Winter Y, Rohrmann S, Linseisen J, Lanczik O, Ringleb PA, Hebebrand J, Back T. Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. Stroke 2008;39:3145–51.
[9] Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssönen K, Salonen JT. Metabolic syndrome and the risk of stroke in middle-aged men. Stroke 2006;37:806–11.
[10] Kjeldsen SEJ, Julies S, Hedner T, Hansson L. Stroke is more common than myocardial infarction in hypertension: analysis based on 11 major randomized intervention trials. Blood Press 2001;10:190–2.
[11] Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol 2003;2:43–53.
[12] Ayala C, Croft JB, Greenlund KJ, Keenan NL, Donehoo RS, Malarcher AM, Mensah GA. Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995–1998. Stroke 2002;33:1197–201.
[13] Nabavi S, Dean O, Turner A, Sureda A, Daglia M, Nabavi S. Oxidative stress and post-stroke depression: possible therapeutic role of polyphenols? Curr Med Chem 2015;22:343–51.
[14] Nabavi S, Turner A, Dean O, Sureda A, Nabavi S. Post-stroke depression therapy: where are we now? Curr Neurovasc Res 2014;11:279–89.
[15] Slomski A. Insomnia increases stroke risk. JAMA 2014;311:2056.
[16] Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment, and depression: a meta-analysis. Ann Neurol 2013;74:580–91.
[17] Weimar C, Kraywinkel K, Rödl J, Hippe A, Harms L, Kloth A, Diener HC. Etiology, duration, and prognosis of transient ischemic attacks: an analysis from the German Stroke Data Bank. Arch Neurol 2002;59:1584–8.
[18] Saver JL, Johnston KC, Homer D, Wityk R, Koroshetz W, Truskowski LL, Haley EC. Infarct volume as a surrogate or auxiliary outcome measure in ischemic stroke clinical trials. Stroke 1999;30:293–8.
[19] Jacobsen B, Oda K, Knutsen S, Fraser G. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976–88. Int J Epidemiol 2009;38:245–52.
[20] Wang J, Ruotsalainen S, Moilanen L, Lepistö P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007;28:857–64.
[21] Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukocyte Biol 2010;87:779–89.
[22] Chen H, Yoshioka H, Kim GS, Jung JE, Okami N, Sakata H, Maier CM, Narasimhan P, Goeders CE, Chan PH. Oxidative stress in ischemic brain damage: mechanisms of cell death and potential molecular targets for neuroprotection. Antioxid Redox Signal 2011;14:1505–17.
[23] Nabavi SM, Daglia M, Moghaddam AH, Nabavi SF, Curti V. Tea consumption and risk of ischemic stroke: a brief review of the literature. Curr Pharm Biotechnol 2014;15:298–303.
[24] Griep LO, Verschuren WM, Kromhout D, Ocké MC, Geleijnse JM. Raw and processed fruit and vegetable consumption and 10-year stroke incidence in a population-based cohort study in the Netherlands. Eur J Clin Nutr 2011;65:791–9.
[25] Hjartåker A, Knudsen MD, Tretli S, Weiderpass E. Consumption of berries, fruits and vegetables and mortality among 10,000 Norwegian men followed for four decades. Eur J Nutr 2014. http://dx.doi.org/10.1007/s00394-014-0741-9.
[26] Hu D, Huang J, Wang Y, Zhang D, Qu Y. Fruits and vegetables consumption and risk of stroke a meta-analysis of prospective cohort studies. Stroke 2014;45:1613–9.
[27] Lin Y, Chen F, Zhang J, Wang T, Wei X, Wu J, Feng Y, Dai Z, Wu Q. Neuroprotective effect of resveratrol on ischemia/reperfusion injury in rats through TRPC6/CREB pathways. J Mol Neurosci 2013;50:504–13.
[28] Sinha K, Chaudhary G, Kumar Gupta Y. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. Life Sci 2002;71:655–65.
[29] Yang C, Zhang X, Fan H, Liu Y. Curcumin upregulates transcription factor Nrf2, HO-1 expression and protects rat brains against focal ischemia. Brain Res 2009;1282:133–41.
[30] Shutenko Z, Henry Y, Pinard E, Seylaz J, Potier P, Berthet F, Girard P, Sercombe R. Influence of the antioxidant quercetin *in vivo* on the level of nitric oxide determined by electron paramagnetic resonance in rat brain during global ischemia and reperfusion. Biochem Pharmacol 1999;57:199–208.
[31] Nabavi SF, Daglia M, Moghaddam AH, Habtemariam S, Nabavi SM. Curcumin and liver disease: from chemistry to medicine. Compr Rev Food Sci Food Saf 2014;13:62–77.
[32] Nabavi SM, Nabavi SF, Eslami S, Moghaddam AH. *In vivo* protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem 2012;132:931–5.
[33] Nabavi SF, Nabavi SM, Mirzaei M, Moghaddam AH. Protective effect of quercetin against sodium fluoride induced oxidative stress in rat's heart. Food Funct 2012;3:437–41.
[34] Curti V, Capelli E, Boschi F, Nabavi SF, Bongiorno AI, Habtemariam S, Nabavi SM, Daglia M. Modulation of human miR-17–3p expression by methyl 3-*O*-methyl gallate as explanation of its in vivo protective activities. Mol Nutr Food Res 2014;58:1776–84.
[35] Slemmer JE, Shacka JJ, Sweeney M, Weber JT. Antioxidants and free radical scavengers for the treatment of stroke, traumatic brain injury and aging. Curr Med Chem 2008;15:404–14.
[36] Lakhan SE, Kirchgessner A, Hofer M. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. J Transl Med 2009;7:97–107.
[37] Nabavi SM, Marchese A, Izadi M, Curti V, Daglia M, Nabavi SF. Plants belonging to the genus *Thymus* as antibacterial agents: from farm to pharmacy. Food Chem 2015;173:339–47.
[38] Nabavi SF, Nabavi SM, Moghaddam AH, Naqinezhad A, Bigdellou R, Mohammadzadeh S. Protective effects of *Allium paradoxum* against gentamicin-induced nephrotoxicity in mice. Food Funct 2012;3:28–9.
[39] Nabavi SF, Nabavi SM, Ebrahimzadeh MA, Eslami B, Jafari N. In vitro antioxidant and antihemolytic activities of hydroalcoholic extracts of *Allium scabriscapum* Boiss. & Ky. aerial parts and bulbs. Int J Food Prop 2013;16:713–22.
[40] Alinezhad H, Azimi R, Zare M, Ebrahimzadeh MA, Eslami S, Nabavi SF, Nabavi SM. Antioxidant and antihemolytic activities of ethanolic extract of flowers, leaves, and stems of *Hyssopus officinalis* L. Var. *angustifolius*. Int J Food Prop 2013;16:1169–78.
[41] Nabavi SF, Nabavi SM, Setzer WN, Nabavi SA, Nabavi SA, Ebrahimzadeh MA. Antioxidant and antihemolytic activity of lipid-soluble bioactive substances in avocado fruits. Fruits 2013;68:185–93.
[42] Nabavi SF, Russo GL, Daglia M, Nabavi SM. Role of quercetin as an alternative for obesity treatment: You are what you eat! Food Chem 2015;179:305–10.

[43] Nabavi SF, Nabavi SM, Ebrahimzadeh MA, Jafari N, Yazdanpanah S. Biological activities of freshwater algae, *Spirogyra singularis* Nordstedt. J Aquat Food Prod Technol 2013;22:58–65.
[44] Visioli F, Borsani L, Galli C. Diet and prevention of coronary heart disease: the potential role of phytochemicals. Cardiovasc Res 2000;47:419–25.
[45] Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 1993;342:1007–11.
[46] Park JD, Rhee DK, Lee YH. Biological activities and chemistry of saponins from *Panax ginseng* CA Meyer. Phytochem Rev 2005;4:159–75.
[47] Radad K, Gille G, Liu L, Rausch W-D. Use of ginseng in medicine with emphasis on neurodegenerative disorders. J Pharmacol Sci 2006;100:175–86.
[48] Choi K-T. Botanical characteristics, pharmacological effects and medicinal components of Korean *Panax ginseng* CA Meyer. Acta Pharm Sin 2008;29:1109–18.
[49] Wang J, Li S, Fan Y, Chen Y, Liu D, Cheng H, Gao X, Zhou Y. Anti-fatigue activity of the water-soluble polysaccharides isolated from *Panax ginseng* CA Meyer. J Ethnopharmacol 2010;130:421–3.
[50] Coon JT, Ernst E. Panax ginseng. Drug Saf 2002;25:323–44.
[51] Yun TK. *Panax ginseng*—a non-organ-specific cancer preventive? Lancet Oncol 2001;2:49–55.
[52] Zhou W, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Molecular mechanisms and clinical applications of ginseng root for cardiovascular disease. Med Sci Monit 2004;10:RA187–192.
[53] Vuksan V, Sung MK, Sievenpiper JL, Stavro PM, Jenkins AL, Di Buono M, Lee KS, Leiter LA, Nam KY, Arnason JT, et al. Korean red ginseng (*Panax ginseng*) improves glucose and insulin regulation in well-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutr Metab Cardiovasc Dis 2008;18:46–56.
[54] Kim JH. Cardiovascular diseases and *Panax ginseng*: a review on molecular mechanisms and medical applications. J Ginseng Res 2012;36:16–26.
[55] Shibata S, Fujita M, Itokawa H, Tanaka O, Ishii T. Studies on the constituents of Japanese and Chinese crude drugs: XI. Panaxadiol, a sapogenin of ginseng roots. Chem Pharm Bull 1963;11:759–61.
[56] Fuzzati N. Analysis methods of ginsenosides. J Chromatogr B 2004;812:119–33.
[57] Zhu J, Jiang Y, Wu L, Lu T, Xu G, Liu X. Suppression of local inflammation contributes to the neuroprotective effect of ginsenoside Rb1 in rats with cerebral ischemia. Neuroscience 2012;202:342–51.
[58] Park E-K, Choo M-K, Han MJ, Kim D-H. Ginsenoside Rh1 possesses antiallergic and anti-inflammatory activities. Int Arch Allergy Immunol 2004;133:113–20.
[59] Chen XC, Zhu YG, Zhu LA, Huang C, Chen Y, Chen LM, Fang F, Zhou YC, Zhao CH. Ginsenoside Rg1 attenuates dopamine-induced apoptosis in PC12 cells by suppressing oxidative stress. EurJ Pharmacol 2003;473:1–7.
[60] Fu Y, Ji LL. Chronic ginseng consumption attenuates age-associated oxidative stress in rats. J Nutr 2003;133:3603–9.
[61] Chen X, Salwinski S, Lee TF. Extracts of *Ginkgo biloba* and ginsenosides exert cerebral vasorelaxation via a nitric oxide pathway. Clin Exp Pharmacol Physiol 1997;24:958–9.
[62] Lü J-M, Yao Q, Chen C. Ginseng compounds: an update on their molecular mechanisms and medical applications. Curr Vasc Pharmacol 2009;7:293–302.
[63] He F, Guo R, Wu S-L, Sun M, Li M. Protective effects of ginsenoside Rb1 on human umbilical vein endothelial cells in vitro. J Cardiovasc Pharmacol 2007;50:314–20.
[64] Jin YR, Yu JY, Lee JJ, You SH, Chung JH, Noh JY, Im JH, Han XH, Kim TJ, Shin KS, et al. Antithrombotic and antiplatelet activities of Korean red ginseng extract. Basic Clin Pharmacol Toxicol 2007;100:170–5.
[65] Jeon BH, Kim CS, Park KS, Lee JW, Park JB, Kim KJ, Kim SH, Chang SJ, Nam KY. Effect of Korea red ginseng on the blood pressure in conscious hypertensive rats. Gen Pharmacol Vasc Syst 2000;35:135–41.
[66] Yamamoto M, Uemura T, Nakamura S, Uemiya M, Kumagai A. Serum HDL-cholesterol-increasing and fatty liver-improving actions of *Panax ginseng* in high cholesterol diet-fed rats with clinical effect on hyperlipidemia in man. Am J Chin Med 1983;11:96–101.
[67] Hong SY, Kim JY, Ahn HY, Shin J-H, Kwon O. *Panax ginseng* extract rich in ginsenoside protopanaxatriol attenuates blood pressure elevation in spontaneously hypertensive rats by affecting the Akt-dependent phosphorylation of endothelial nitric oxide synthase. J Agric Food Chem 2012;60:3086–91.
[68] Ni H-X, Yu N-J, Yang X-H. The study of ginsenoside on PPARγ expression of mononuclear macrophage in type 2 diabetes. Mol Biol Rep 2010;37:2975–9.
[69] Ye R, Yang Q, Kong X, Han J, Zhang X, Zhang Y, Li P, Liu J, Shi M, Xiong L, et al. Ginsenoside Rd attenuates early oxidative damage and sequential inflammatory response after transient focal ischemia in rats. Neurochem Int 2011;58:391–8.
[70] Ye R, Li N, Han J, Kong X, Cao R, Rao Z, Zhao G. Neuroprotective effects of ginsenoside Rd against oxygen-glucose deprivation in cultured hippocampal neurons. Neurosci Res 2009;64:306–10.
[71] Liu X, Wang L, Wen A, Yang J, Yan Y, Song Y, Liu X, Ren H, Wu Y, Li Z, et al. Ginsenoside-Rd improves outcome of acute ischaemic stroke—a randomized, double-blind, placebo-controlled, multicenter trial. Eur J Neurol 2012;19:855–63.
[72] Attele AS, Wu JA, Yuan C-S. Ginseng pharmacology: multiple constituents and multiple actions. Biochem Pharmacol 1999;58:1685–93.
[73] Lewis R, Wake G, Court G, Court JA, Pickering AT, Kim YC, Perry EK. Non-ginsenoside nicotinic activity in ginseng species. Phytother Res 1999;13:59–64.
[74] Shi Y, Sun C, Zheng B, Li Y, Wang Y. Simultaneous determination of nine ginsenosides in functional foods by high performance liquid chromatography with diode array detector detection. Food Chem 2010;123:1322–7.
[75] Mihalov JJ, Marderosian AD, Pierce JC. DNA identification of commercial ginseng samples. J Agric Food Chem 2000;48:3744–52.
[76] Lim W, Mudge KW, Vermeylen F. Effects of population, age, and cultivation methods on ginsenoside content of wild American ginseng (*Panax quinquefolium*). J Agric Food Chem 2005;53:8498–505.
[77] Schlag EM, McIntosh MS. Ginsenoside content and variation among and within American ginseng (*Panax quinquefolius* L.) populations. Phytochemistry 2006;67:1510–9.
[78] Yun TK, Lee YS, Lee YH, Kim SI, Yun HY. Anticarcinogenic effect of *Panax ginseng* CA Meyer and identification of active compounds. J Korean Med Sci 2001;16:S6–18.
[79] Yuan C-S, Wu JA, Osinski J. Ginsenoside variability in American ginseng samples. Am J Clin Nutr 2002;75:600–1.
[80] Cheng L-Q, Kim MK, Lee J-W, Lee Y-J, Yang D-C. Conversion of major ginsenoside Rb1 to ginsenoside F2 by *Caulobacter leidyia*. Biotechnol Lett 2006;28:1121–7.
[81] Chi H, Ji G-E. Transformation of ginsenosides Rb1 and Re from *Panax ginseng* by food microorganisms. Biotechnol Lett 2005;27:765–71.
[82] Hsu BY, Lu TJ, Chen CH, Wang SJ, Hwang LS. Biotransformation of ginsenoside Rd in the ginseng extraction residue by fermentation with lingzhi (*Ganoderma lucidum*). Food Chem 2013;141:4186–93.
[83] Kim MK, Lee JW, Lee KY, Yang D. Microbial conversion of major ginsenoside rb ~1 to pharmaceutically active minor Ginsenoside Rd. J Microbiol Seoul 2005;43:456–62.
[84] Son J-W, Kim H-J, Oh D-K. Ginsenoside Rd production from the major ginsenoside Rb1 by β-glucosidase from *Thermus caldophilus*. Biotechnol Lett 2008;30:713–6.
[85] Yu H, Liu H, Zhang C, Tan D, Lu M, Jin F. Purification and characterization of gypenoside-α-l-rhamnosidase hydrolyzing gypenoside-5 into ginsenoside Rd. Process Biochem 2004;39:861–7.
[86] Zhang C, Yu H, Bao Y, An L, Jin F. Purification and characterization of ginsenoside-α-arabinofuranase hydrolyzing ginsenoside Rc into Rd from the fresh root of *Panax ginseng*. Process Biochem 2002;37:793–8.
[87] Zhao X, Wang J, Li J, Fu L, Gao J, Du X, Bi H, Zhou Y, Tai G. Highly selective biotransformation of ginsenoside Rb1 to Rd by the phytopathogenic fungus *Cladosporium fulvum* (syn. *Fulvia fulva*). J Ind Microbiol Biotechnol 2009;36:721–6.
[88] Zhao X, Gao L, Wang J, Bi H, Gao J, Du X, Zhou Y, Tai G. A novel ginsenoside $Rb_1$-hydrolyzing β-D-glucosidase from *Cladosporium fulvum*. Process Biochem 2009;44:612–8.
[89] Kochkin DV, Kachala VV, Shashkov AS, Chizhov AO, Chirva VY, Nosov AM. Malonyl-ginsenoside content of a cell-suspension culture of *Panax japonicus* var. *repens*. Phytochemistry 2013;93:18–26.
[90] Wang J, Man S, Gao W, Zhang L, Huang L. Cluster analysis of ginseng tissue cultures, dynamic change of growth, total saponins, specific oxygen uptake rate in bioreactor and immuno-regulative effect of ginseng adventitious root. Ind Crops Prod 2013;41:57–63.
[91] Ye R, Kong X, Yang Q, Zhang Y, Han J, Zhao G. Ginsenoside Rd attenuates redox imbalance and improves stroke outcome after focal cerebral ischemia in aged mice. Neuropharmacology 2011;61:815–24.
[92] Ye R, Zhang X, Kong X, Han J, Yang Q, Zhang Y, Chen Y, Li P, Liu J, Shi M, et al. Ginsenoside Rd attenuates mitochondrial dysfunction and sequential apoptosis after transient focal ischemia. Neuroscience 2011;178:169–80.
[93] Zhang Y, Zhou L, Zhang X, Bai J, Shi M, Zhao G. Ginsenoside-Rd attenuates TRPM7 and ASIC1a but promotes ASIC2a expression in rats after focal cerebral ischemia. Neurol Sci 2012;33:1125–31.
[94] Li XY, Liang J, Tang YB, Zhou JG, Guan YY. Ginsenoside Rd prevents glutamate-induced apoptosis in rat cortical neurons. Clin Exp Pharmacol Physiol 2010;37:199–204.
[95] Zhang X, Shi M, Bjørås M, Wang W, Zhang G, Han J, Liu Z, Zhang Y, Wang B, Chen J, et al. Ginsenoside Rd promotes glutamate clearance by up-regulating glial glutamate transporter GLT-1 via PI3K/AKT and ERK1/2 pathways. Front Pharmacol 2013;4:152–60.
[96] Hu G, Wu Z, Yang F, Zhao H, Liu X, Deng Y, Shi M, Zhao G. Ginsenoside Rd blocks AIF mitochondrio-nuclear translocation and NF-κB nuclear accumulation by inhibiting poly(ADP-ribose) polymerase-1 after focal cerebral ischemia in rats. Neurol Sci 2013;34:2101–6.
[97] Zhang X, Shi M, Ye R, Wang W, Liu X, Zhang G, Han J, Zhang Y, Wang B, Zhao J, et al. Ginsenoside Rd attenuates Tau protein phosphorylation via the PI3K/AKT/GSK-3β pathway after transient forebrain ischemia. Neurochem Res 2014:1–11.
[98] Liu X, Xia J, Wang L, Song Y, Yang J, Yan Y, Ren H, Zhao G. Efficacy and safety of ginsenoside-Rd for acute ischaemic stroke: a randomized, double-blind, placebo-controlled, phase II multicenter trial. Eur J Neurol 2009;16:569–75.