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Review

Ginsenoside Rb1 as a neuroprotective agent: A review

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ABSTRACT

Ginsenosides represent the major bioactive components of ginseng. These triterpenoid saponins have been shown to exert numerous beneficial effects on the human body. Recent evidences suggest that ginsenosides may be useful for the management and treatment of several diseases of the central nervous system (CNS). In particular, numerous *in vitro* and *in vivo* models have shown that ginsenosides can modulate numerous pharmacological effects on the brain, including attenuation of excitotoxicity, oxidative stress and neuroinflammation, maintenance of neurotransmitter balance, anti-apoptotic effects, and mitochondrial stabilization effects. Regulations of these pathophysiological mechanisms have been shown to improve cognitive function and protect the brain against several neurodegenerative diseases. This review will critically address the pharmacological effects and mechanisms of action of ginsenosides in the CNS, and particularly those associated with therapeutic efficacies in Parkinson's disease, Alzheimer's disease, Huntington's disease, and traumatic brain injury, and ischemia.

Contents

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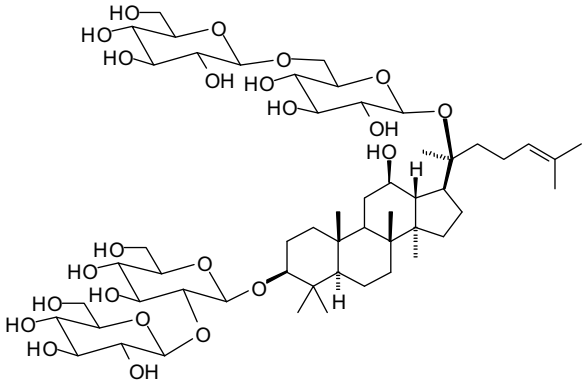

Fig. 1. Molecular structure of ginsenoside Rb1.

1. Introduction

Ginseng has been used as a medicinal plant in Manchuria (modern day China) for over 5000 years. While its roots have been consumed as foods, early Chinese used ginseng as a tonic to improve the body's resilience to exogenous and endogenous stressors, and maintain normal cellular homeostasis (Nocerino et al., 2000). However, it was not until the middle of the last century that scientists in the developed world attempted to isolate bioactive components from ginseng. Subsequent studies led to the identification of several ginsenosides, which have been attributed to the beneficial effects of ginseng consumption on several body systems (Van Kampen et al., 2003).

Ginsenosides are unique triterpenoid saponin that is distributed exclusively to the genus Panax in the family Araliaceae (Sanada et al., 1974; Shi et al., 2007). Over 150 naturally occurring ginsenosides have been isolated from roots, stems, leaves, flowers and fruits of the ginseng plant (Liu and Xiao, 1992). All ginsenosides share a common four-ring hydrophobic structure (Chen et al., 2009). However, the number of sugar moieties may vary among ginsenosides. Ginsenosides are classified into two main groups depending on the number and position of these sugar moieties: 20(*S*)-protopanaxadiol (PD), and 20(*S*)-protopanaxatriol (PT) saponins. It is thought that the variability of the sugar component may be associated with the specific action of each ginsenosides (Nah et al., 1995).

Recent studies have shown that ginsenosides may exert beneficial therapeutic effects in several degenerative diseases, including cardiovascular disease (Lee and Kim, 2014), cancer (Lee et al., 2015), glaucoma (Wang et al., 2015), and stroke (Brassai et al., 2015; Dong et al., 2015; Kim et al., 2014; Lv et al., 2015; Miao et al., 2015). Ginsenosides also demonstrate favourable pharmacological effects in the central nervous system (CNS) which may be therapeutically translated to the clinic. Ginsenosides have been shown to enhance brain function, protect against oxidative stress and neuroinflammation, and slow down or attenuate numerous neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, Huntington's disease, and traumatic brain injury (Liu and Xiao, 1992; Nah et al., 1995; Nocerino et al., 2000; Van Kampen et al., 2003). This review summarises evidence for the effects of ginsenosides in several pathologies of the CNS, and the clinical implications of ginsenosides in the brain.

2. Sources and biosynthesis of ginsenoside Rb1

The primary sources of ginsenoside Rb1 are members of the *Panax* genus, *Panax ginseng* (Asian ginseng) (Sanada et al., 1974; Shi et al., 2007), *Panax quinquefolius* (American ginseng) (Qi et al., 2011; Schlag and McIntosh, 2006), and *Panax notoginseng* (Wan et al., 2006a,b) (see Table 1). Ginsenoside Rb1 has been found in higher concentrations in *P. quinquefolius* and *P. notoginseng* (around 2–4%) roots than in *P. ginseng* root (around 0.2–0.8%). Stems and leaves of *Panax* spp. generally have lower concentrations of ginsenoside Rb1 than the roots, rhizomes, or root hairs. Ginsenosides, including ginsenoside Rb1, have been isolated from root cultures of *P. ginseng* (Mallol et al., 2001). Thus, callus cultures of *P. ginseng* root have yielded as much as 2.12% ginsenoside Rb1.

The biosynthesis of ginsenosides has been reviewed (Liang and Zhao, 2008; Wang et al., 2012), but we briefly summarize the biosynthesis of ginsenoside Rb1. Ginsenoside Rb1 {(3β,12β,20*S*)-dammar-24-ene-3,12,20-triol, 3-*O*-[β-d-glucopyranosyl-(1 → 2)-β-d-glycopyranoside], 20-*O*-[β-d-glucopyranosyl-(1 → 6)-β-d-glucopyranoside]} (see Fig. 1), a triterpenoid saponin, is biosynthesized by way of 2,3-oxidosqualene cyclization (Fig. 2). The isoprene precursors for the terpenoids, isopentenyl diphosphate (Diestel et al., 2003) and dimethylallyl diphosphate (DMAPP) are formed by either, or both, the mevalonate (MVA) pathway (Dey and Harborne, 1997) or the methylerythritol phosphate (MEP pathway) (Lichtenthaler, 1999). Geranyl diphosphate synthase (*GPS*) catalyzes the condensation between IPP and DMAPP to form geranyl diphosphate (GPP). GPP is converted to farnesyl diphosphate (FPP) by condensation with IPP catalyzed by farnesyl diphosphate synthase (*FPS*). The condensation of two FPP moieties, catalyzed by squalene synthase (*SS*), gives squalene. Squalene is oxidized by squalene epoxidase (*SE*) to give 2,3-oxidosqualene. Cyclization of 2,3-oxidosqualene by dammarenediol synthase (*DSS*) can give dammarenediol II, which is oxidized by cytochrome P450 (*CYP*) to protopanaxadiol. Ginsenoside Rb1 is synthesized by adding four glucose moieties to the triterpenoid by glucosyltransferase (*GT*) enzymes.

3. Bioavailability and metabolism of ginsenoside Rb1

Using a rat model, Akao et al. (1998) have demonstrated that ginsenoside Rb1 is poorly absorbed from the gut, but undergoes deglucosylation by intestinal bacteria to give secondary ginsenoside compound K by way of ginsenosides Rd and F_2 (Fig. 3). Similarly, Niu et al. (2013) have observed that ginsenoside Rb1 was hydrolyzed by mouse intestinal microbes to give ginsenoside compound K by stepwise hydrolysis with formation of ginsenoside F_2 from ginsenoside Rd as the rate-limiting step in the biotransformation. It has been shown that in humans, orally-ingested ginsenoside Rb1 is not hydrolyzed in the stomach or small intestine, but is hydrolyzed by intestinal bacterial (*Eubacterium* sp. A-44, *Fusobacterium* sp. K-60 *Prevotella oris*, *Streptococcus* sp., *Bacteriodes* sp. JY-6, and *Bifidobacterium* sp.) β-glucosidases (Hasegawa, 2004; Kim, 2009; Tawab et al., 2003)(Fig. 3). The hydrolyzed metabolite, compound K, is then absorbed and undergoes enterohepatic circulation. In the liver, compound K is excreted in bile or conjugated with fatty acids at either C(3) or C(6) of the glucose moiety. Apparently the fatty-acid derivatives are not excreted in the bile but can accumulate in the liver (Kim, 2009). Interestingly, ginsenoside Rb1 has been