Biotransformation, Pharmacokinetics, and Pharmacological Activities of Ginsenoside Rd Against Multiple Diseases

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Panax ginseng C.A. Mey. has a history of more than 4000 years and is widely used in Asian countries. Modern pharmacological studies have proved that ginsenosides and their compounds have a variety of significant biological activities on specific diseases, including neurodegenerative diseases, certain types of cancer, gastrointestinal disease, and metabolic diseases, in which most of the interest has focused on ginsenoside Rd. The evidentiary basis showed that ginsenoside Rd ameliorates ischemic stroke, nerve injury, cancer, and other diseases involved in apoptosis, inflammation, oxidative stress, mitochondrial damage, and autophagy. In this review, we summarized available reports on the molecular biological mechanisms of ginsenoside Rd in neurological diseases, cancer, metabolic diseases, and other diseases. We also discussed the main biotransformation pathways of ginsenoside Rd obtained by fermentation.

Keywords: Panax ginseng C.A. Mey., ginsenoside Rd, biotransformation, pharmacokinetics, molecular mechanisms

HIGHLIGHTS
1) Approximately 120 studies on the use of ginsenoside Rd for the treatment of multiple diseases have been published.
2) This is the first review to report about the biotransformation, pharmacokinetics, and pharmacological effects of ginsenoside Rd.
3) The potential pharmacological mechanisms of ginsenoside Rd have been documented.
4) No specific reviews have been conducted by now.

INTRODUCTION

Panax ginseng C.A. Mey. is a well-known herbal medicine widely used in China, Korea, Japan, and other East Asian countries. At present, the ginseng root and its extract are the most widely used herbal medicine. Modern pharmacological studies have proved that ginsenosides are the main active ingredient of ginseng and have a wide range of pharmacological effects, such as anti-inflammatory...
(Xu et al., 2021; Yi, 2021), anticancer (Zhang et al., 2021a), and anti-viral (Kang et al., 2021), regulate immunity (Kang et al., 2021), metabolism (Wang et al., 2021a), and improve cardiovascular system (Wang et al., 2021b; Sarhene et al., 2021) and nervous system (Brioschi Guevara et al., 2021) function, whereas most attention has been focused on the ginsenoside Rd.

Ginsenoside Rd, a natural compound extracted from the root of Panax ginseng C.A. Mey., is one of the protopanaxadiol (PPD)-type ginsenosides, while the proportion of ginsenoside Rd in ginseng is very low (Liu et al., 2020a). Interestingly, the promising effects of the pretreatment and treatment of ginsenoside Rd on neurological diseases, cancer, gastrointestinal disease, and metabolic diseases have been studied extensively in in vivo and in vitro models (Guo et al., 2021; Chen et al., 2022; Zhou et al., 2022).

Existing studies related to ginsenoside Rd have shown that various ginsenosides, such as Rb1, Rb2, and Rc, can be transformed into ginsenoside Rd after absorption and metabolism in vivo (Park et al., 2010; Shin and Oh, 2016). In addition, Rd can be prepared in a variety of ways based on the in-depth study of biotransformation and the development of modern fermentation technology (He et al., 2019). Based on the above results, we summarized the biotransformation process of other ginsenosides into Rd, thereby hoping to play a positive role in the large-scale industrial production of Rd. In this study, the biotransformation sources, pharmacokinetics, pharmacological effects, and molecular mechanisms of ginsenoside Rd on various systemic diseases in recent years were reviewed, and their therapeutic potential was discussed.

**BIOTRANSFORMATION OF GINSENOSIDE RD**

Multiple studies have confirmed that ginsenosides can be transformed into ginsenoside Rd using enzymes and bacterial communities and can promote the transformation of ginsenoside
et al., 2013; Zhang et al., 2021b). AbpBs can promote the position of ginsenoside Rc into ginsenoside Rd by attacking the C-20 hydroxyl group of ginsenoside compound K (CK) to form ginsenoside compound (Jung et al., 2014). In addition, enzymes PgUGT74AE2 and PgUGT94Q2, which participate in ginsenoside biosynthesis, transfer two glucose groups from UDP-glucose (UDP-Glc) to the C3 hydroxyl group of ginsenoside compound (CK) to form ginsenoside Rd (Jung et al., 2014). β-glucosidase cleaves the glycoside at the C-3 position of ginsenoside Rd and produces the ginsenoside compound CK (Jung et al., 2014).

| References | Conversion | Source | Enzyme | Optimal conditions | Conversion ratio (%) |
|------------|------------|--------|--------|--------------------|---------------------|
| Akter and Huq (2018) | Rb1 to Rd | Paenibacillus | MAH-16T | pH 5.0-7.0, 20-40°C | 46.15 |
| Fang et al. (2020) | Rb1 to Rd | Dekkera anomala YAE-1 | Pectinase | pH 6.0, 52.5°C | 92.44 |
| Rencinkhand et al. (2017) | Rb1 to Rd | Flavobacterium johnsoniae | β-glucosidase | pH 7.0, 37°C, 14 days | 92.44 |
| Quan et al. (2011) | Rb1 to F2 | Bacillus subtilis | β-glucosidase | pH 6.0, 37°C, 14 days | 92.44 |
| Son et al. (2008) | Rb1 to Rd | Thermus caldophilus | β-glucosidase | pH 5.0, 75°C, 18 h | 92.44 |
| Kim et al. (2013a) | Rb1 to Rd | Microbacterium trichothececentlycum | KCTC 19343 | pH 5.0, 37°C, 8 days | 92.44 |
| Zhao et al. (2009) | Rb1 to Rd | Cladosporium fulvum | β-glucosidase | pH 5.0, 37°C, 8 days | 92.44 |
| Lin et al. (2015) | Rb1 to Rd | Aspergillus versicolor LFJ1403 | β-glucosidase | pH 5.0, 37°C, 14 days | 92.44 |
| Shin et al. (2013) | Rc to Rd | Caldicellulosiruptor saccharolyticus | a1-L-arabinofuranosidase | pH 5.0, 30°C, 60 min | 92.44 |
| Xie et al. (2016a) | Rc to Rd | Thermostoga thermarum DSM5069 | a1-L-arabinofuranosidase | pH 5.0, 30°C, 60 min | 92.44 |
| Liu et al. (2013) | Rc to Rd | Leuconostoc sp. strain 22-3 | a1-L-arabinofuranosidase | pH 5.0, 30°C, 60 min | 92.44 |
| Zhang et al. (2021b) | Rc to Rd | Bacillus subtilis Str. 188 | a1-L-arabinofuranosidase | pH 5.0, 40°C, 4 h | 92.44 |
| Kim et al. (2020) | Rb2 to Rd | Blastococcus saxobsidens | a1-L-arabinopyranosidase | pH 5.0, 30°C, 4 h | 92.44 |
| Jung et al. (2014) | F2 to Rd | Ginseng UDP-glycosyltransferases | UDP-glycosyltransferases 94Q2 | pH 5.0, 40°C, 4 h | 92.44 |

Rd into other metabolites (He et al., 2019). We summarized the precursors, metabolites, and transformation conditions of ginsenoside Rd (Table 1) (Figure 1).

Ginsenoside Rd can be synthesized from ginsenoside Rb1 by the hydrolysis of glucose at C-20 (Akter and Huq, 2018). The β-glucosidase produced by pectinase (Fang et al., 2020), Dekkera anomala YAE-1 (Rencinkhand et al., 2020), Paenibacillus sp. MBT213 (Rencinkhand et al., 2017), Flavobacterium johnsoniae (Hong et al., 2012), Leuconostoc mesenteroides DC102 (Quan et al., 2011), and Lactobacillus brevis (Zhong et al., 2016) are able to hydrolyze ginsenoside Rb1 (Rb1) and convert it to ginsenoside Rd during the fermentation of the ginseng. In addition, Aspergillus niger strain TH-10 (Feng et al., 2016), Paecilomyces bainier 229-7 (Ye et al., 2010), Thermococcus kotsenii (Son et al., 2008), Microbacterium trichothececentlycum (Kim et al., 2013a), Cladosporium fulvum (Zhao et al., 2009), and Aspergillus versicolor (Lin et al., 2015) have shown similar effects as those of hydrolyses in Rb1.

The a1-L-arabinosidase (AbpBs) from Caldicellulosiruptor saccharolyticus (Shin et al., 2013), Thermotoga thermarum DSM 5069 (Xie et al., 2016a), Leuconostoc sp. 22-3 (Liu et al., 2013), and Bacillus subtilis (Zhang et al., 2021b) converts ginsenoside Rc (Rc) into ginsenoside Rd by attacking the C-20 position of α-linked arabinoside, thereby releasing arabinosae (Liu et al., 2013; Zhang et al., 2021b). AbpBs can promote the biotransformation of ginsenoside Rb2 (Rb2) to ginsenoside Rd by attacking C-20, thereby releasing arabinosae (Kim et al., 2020). In addition, enzymes PgUGT74AE2 and PgUGT94Q2, which participate in ginsenoside biosynthesis, transfer two glucose groups from UDP-glucose (UDP-Glc) to the C3 hydroxyl group of ginsenoside compound K (CK) to form ginsenoside Rd (Jung et al., 2014).

β-glucosidase cleaves the glycoside at the C-3 position of ginsenoside Rd and produces the ginsenoside compound CK (Jung et al., 2014). Ginsenoside M1 is formed by the hydrolysis of the C3 glucose group in ginsenoside Rd by snailase (Renchinkhand et al., 2017).

PHARMACOKINETICS

Intestinal flora can promote the metabolic transformation of ginseng extract and Rb1 into ginsenoside Rd in rats and can enter the blood for absorption in rats (Kim et al., 2014a). Ginsenoside Rd is distributed in various organs, with the highest content in the lungs, followed by the liver, kidney, heart, and intestine, and the lowest content in the brain (Sun et al., 2012). After taking urine 0–24 h after oral administration and intravenous administration, liquid chromatography-mass spectrometry (LC-MS) is used to confirm that oxidation and
### TABLE 2 | Summary of the neuroprotective effects and mechanism of ginsenoside Rd in animal and cell models.

| References                  | Diseases                  | Inducer | Experimental model | Effects                                      | Mechanism                           |
|-----------------------------|---------------------------|---------|--------------------|----------------------------------------------|--------------------------------------|
| Zhang et al. (2013a)        | Ischemic stroke           | MCAO    | Male SD rats       | GLT-1, PKB/Akt, p-ERK1/2↑                    | Glutamate metabolism                |
| Zhang et al. (2012a)        | Ischemic stroke           | Glutamate, NMDA | Primary hippocampal cell cultures from SD rat embryos | TUNEL-positive cells, caspase-3, Ca2+↓ | Ca2+; apoptosis                      |
| Xie et al. (2016b)          | Stroke                    | OGD/Transient MCAO | Adult male primary cortical neuron cells/SD rats | Infarct volume, NR2B subunit, p-Ser-1303, p-Tyr-1472, p-Tyr-1480↓ | Hyperphosphorylation of neurons     |
| Zhang et al. (2020a)        | Ischemic stroke           | OGD/MCAO, CsA | Primary cortical neurons cells, HEK293 cells/Adult male SD rats | Ca2+↑, NMDA receptor currents, caspase3↓ | Apoptosis                            |
| Zhang et al. (2012b)        | Ischemic stroke           | MCAO    | Male SD rats       | ASIC2a↑                                     | Ca2+ overload                        |
| Ye et al. (2011b)           | Transient ischemic stroke | MCAO    | Male SD rats, isolated mitochondria                | Mitochondrial dysfunction, apoptosis  |
| Yang et al. (2016)          | Ischemic stroke           | MCAO    | Male SD rats       | NEIL1, NEIL3↑                                | mtDNA and nDNA damages, apoptosis    |
| Hu et al. (2013)            | Cerebral ischemia         | MCAO    | Adult male SD rats | PARP-1, NE-β, AIF↓                          | Apoptosis, inflammation              |
| Ye et al. (2009)            | Cerebral ischemic injury  | OGD     | Primary hippocampal neurons cells                   | ROS, MdA/LDH, GSSG↑                  | Oxidative stress, apoptosis          |
| Ye et al. (2011c)           | Transient focal ischemia  | MCAO    | Male C57BL/6 mice | Mitochondrial complex, MMP, CAT, SOD, GPX, GST↑ | Mitochondrial dysfunction oxidative stress |
| Zhang et al. (2014)         | Ischemic stroke           | OGD/MCAO | Primary culture of neurons/Male SD rats | p- Akt, GSK3-β↑                        | p-tau                                |
| Liu et al. (2015a)          | Stroke                    | OGD/R/Transient MCAO followed by reperfusion | PC12 cells/Male SD rats | p-tau, S199/202, PHF-1↓                      | Apoptosis                            |
| Hou et al. (2017)           | TMT intoxication          | Trimehtyltin | Primary hippocampal neuron/Male ICR mice | Bcl-2↑                                 | Apoptosis                            |
| Ye et al. (2011d)           | Transient ischemic stroke | MCAO    | Male SD rats       | CAT, SOD 1 and 2, GR, GSH/ GSSG↓, 2,3- and 2,5-DHBA, 8-OHdG↑, positive cells, 4-HNE, MDA, AGE↓ | Oxidative stress, inflammation      |
| Zhang et al. (2020b)        | Transient forebrain ischemia | MCAO | Male SD rats | IkB-α↑                                    | Inflammation                         |
| Zhang et al. (2016)         | Ischemic stroke           | OGD or LPS/MCAO | BV2 cells/Adult male SD rats | p- Akt, GSK3-β↑, p- IκBα, p-kBα, IL-6↑, TNF-α↑, IFN-γ↑, | p- Akt, GSK3-β↑, p- IκBα, p-kBα, IL-6↑, TNF-α↑, IFN-γ↑, | Inflammation                         |
| Wu et al. (2016)            | Ischemic stroke           | NGF     | PC12 cells        | p-ERK1/2, p AKT, p-Akt↑                      | NGF                                  |
| Ye et al. (2008)            | Oxidative damage          | H2O2    | PC12 cells        | SOD, GPX, MMP↑                             | Oxidative stress, mitochondrial dysfunction |
| Ren et al. (2021)           | GBS                       | Peripheral nerve antigen P0, 30-100 Peptide, Pertussis toxin (PTX) | Male C57 BL/6 mice | Non-classical Ly6C<sup>hi</sup> monocytes, 20S proteasome, NF-κB<sup>b</sup>, p65, matrix MMP-9<sup>b</sup> | Inflammation                          |
| Liu et al. (2015b)          | Parkinson disease         | MPP     | SH-SYS5 cells/C57BL/ 6J mice | SOD, GPX, MMP, complex I, ATP, Bcl-2, p-Akt↑ | Oxidative stress, mitochondrial dysfunction |
| Liu et al. (2015c)          | Alzheimer’s disease       | Aβ<sub>25-35</sub> | Primary cultured hippocampal neurons cells | SOD, Bax mRNA, Caspase-3, Cyt C mRNA↑ | Oxidative stress, Neuronal apoptosis |
| Liu et al. (2015d)          | Alzheimer’s disease       | APP transgenic mice | APP transgenic mice | IL-1β, IL-6, TNF-α, S100β<sup>b</sup> mRNA, NF-κB<sub>b</sub> p65<sup>b</sup> | IL-10↑ | Inflammation |
| Kim et al. (2014b)          | Neurodegenerative diseases | Neuro2a cells | Neuro2a cells | ChAT, VACHT, Ach, MAP-2, p75, p21, TrkA↑ | Cholinergic markers |
| Li et al. (2013)            | Alzheimer’s disease       | APP transgenic mice | APP transgenic mice | Ser9, PP-2A↑ | p-tau |

(Continued on following page)
TABLE 2 | (Continued) Summary of the neuroprotective effects and mechanism of ginsenoside Rd in animal and cell models.

| References | Diseases | Inducer | Experimental model | Effects | Mechanism |
|------------|----------|---------|--------------------|---------|-----------|
| Li et al. (2011a) | Alzheimer’s disease | Okadaic Acid | Adult male SD rats/ APP transgenic mice | GSK-3β, Tyr216↓, PP-2A↑ | Tau |
| Li et al. (2021) | Alzheimer’s disease | Ovariectomy/Inhibitor | Adult female rats/HT22 hippocampal neuronal cells | BACE1, Aβ↓, sAPPα, ADAM↑ | Activating estrogen-like activity |
| Yan et al. (2017) | Alzheimer’s disease | Ovariectomy/Inhibitor | Adult female rats/HT22 hippocampal neuronal cells | BACE1, Aβ↓, sAPPα, ADAM↑ | Activating estrogen-like activity |
| Zhu et al. (2014) | Multiple sclerosis | Experimental autoimmune encephalomyelitis | 6-8 weeks female CS7BL/6 mice | IL-4, BDNF, NGF↑ | Blood-brain barrier, inflammation |
| Jn et al. (2020a) | Multiple sclerosis | Experimental autoimmune encephalomyelitis | Splenocyte/6-8 weeks CS7BL/6 mice | TGF-β↓, IL-10, Treg, Foxp3↑ | Inflammation, autoimmunity |
| Cong and Chen, (2016) | Spinal cord injury | T8 laminectomy and a spinal contusion injury | Adult female SD rats | MDA, TNF-α, IL-1β, IL-6, Bax, GSK, SOD, Bcl-2↑, cleaved-caspase 3, p-ERK↑, p-JNK, p-p38↑, p- Akt, p-ERK↑ | Oxidative stress, inflammation, apoptosis |
| Zhou et al. (2014) | Paraplegia | Ca2+ | Isolated spinal cord mitochondria/Male CS7BL/6J mice | Cyto C↓ | Mitochondrial dysfunction |
| Wang et al. (2014) | Delayed paralysis | Occlusion of the abdominal aorta for 1 h | Female SD rats | Caspase 3, ASK1, JNK↑ | Apoptosis |
| Wang et al. (2020) | Cognitive impairment | Respiration in a transparent Plexiglas restrainer with many air holes to for 10 h | Male CS7BL/6J mice | SOD, CAT, GSH, GPX, p-Pi3K, p-CREB, BDNF, TrkB↑ | Oxidative stress, inflammation, neurotrophic factors |
| Wang et al. (2013a) | Lead (Pb) exposure | Retired breeder SD rats | | NF-κB, IkBα, NFAT↑ | Inflammation |

Abbreviations: CsA, cyclosporin A; ETC, mitochondrial electron transport chain; CAT, catalase; SOD, superoxide dismutase; GPX, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSSG, glutathione disulfide; 8-OHdG, 8-hydroxy-deoxyguanosine; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; AGEs, advanced glycosylation end products; NDF, nerve growth factor; PTX, pertussis toxin; Nr4a1, nuclear receptor subfamily 4 group A member 1; ChAT, choline acetyltransferase; VACHT, vesicular acetylcholine transporter; ACh, acetylcholine.

glycosylation (Yang et al., 2006a; Yang et al., 2007a) are the main metabolic pathways of ginsenoside Rd in rats. The absolute bioavailability of Rd in dogs is 0.26% (Wang et al., 2007). As in clinical trials, ginsenoside Rd shows linear pharmacokinetics, is well tolerated in the dose range of 10–75 mg after an intravenous administration, and is slowly cleared from plasma, and the elimination rate does not change after repeated administration (Zeng et al., 2010).

GINKGOSIDE RD TARGETS MULTIPLE DISEASES

Ischemic Stroke
In ischemic stroke, ginsenoside Rd plays a neuroprotective role by restoring mitochondrial function, reducing neuronal apoptosis, and eliminating neuroinflammation (Figure 2). As for the therapeutic window study, ginsenoside Rd shows an obvious neuroprotective effect in the middle cerebral artery occlusion (MCAO) model (Ye et al., 2011a). Importantly, the results of a clinical trial showed that ginsenoside Rd has a positive effect on the prognosis of acute ischemic stroke (Liu et al., 2012).

In Ca2+ influx and mitochondrial dysfunction, ginsenoside Rd, a potential Ca2+ channel blocker (Liang et al., 2010), significantly reduces the burst of glutamate by increasing the expression of glutamate transporter-1 (GLT-1) and inhibits the channels of Ca2+ influx (Zhang et al., 2013a) to protect the rat hippocampal neurons (Zhang et al., 2012a). Similar to a calcineurin inhibitor, ginsenoside Rd exerts a neuroprotective effect by inhibiting the elevation of N-methyl-D-aspartate (NMDA) receptors and the hyperphosphorylation of the N-methyl-D-aspartate receptor 2B (NR2B) subunit in the MCAO model and oxygen–glucose deprivation (OGD) cultured neurons (Xie et al., 2016b; Zhang et al., 2020a). Ginsenoside Rd pretreatment exerts neuroprotective effects by inhibiting the Ca2+ overload and specificity attenuated the expression of transient receptor potential melastatin (TRPM) 7 and acid-sensing ion channel (ASIC) 1a while promoting ASIC2a expression following focal ischemia (Zhang et al., 2012b). Remarkably, the results of a clinical trial based on Ca2+ disorder and subsequent neurotoxicity induced by acute ischemic stroke, ginsenoside Rd can be considered a calcium channel antagonist and a neuroprotectant (Liu et al., 2009). As for mitochondrial dysfunction, ginsenoside Rd markedly protects the mitochondria, as indicated by regulating enzyme activity, reducing mitochondrial hydrogen peroxide production and depolarizing mitochondrial membrane potential (MMP), decreasing reactive oxygen species (ROS) production in isolated mitochondria from Sprague–Dawley (SD) rats (Ye et al., 2011b), and reducing the mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) damage and cell apoptosis in MCAO-induced stroke model (Hu et al., 2013; Yang et al., 2016).
These findings are also confirmed in primary cultured hippocampal neuron cells (Ye et al., 2009). In addition, in elderly stroke mice, ginsenoside Rd can play an equivalent neuroprotective role in elderly transient focal ischemic mice by regulating lipid peroxide accumulation, mitochondrial complex activity, and MMP (Ye et al., 2011c).

As far as apoptosis is concerned, ginsenoside Rd may reduce cerebral ischemia-induced tau phosphorylation by decreasing the activity of glycogen synthase kinase-3β (GSK-3β) and enhancing the activity of protein kinase B (PKB/AKT) (Zhang et al., 2014). In PC12 cells with OGD/reperfusion (OGD/R) and SD rats with ischemia/reperfusion (I/R) injury, ginsenoside Rd significantly limits the expression of vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and the phosphatidylinositol 3-kinase (PI3K)/AKT and ERK1/2 pathways (Liu et al., 2015a). As a neuroprotective agent ginsenoside Rd also prevents trimethyltin (TMT)-induced neurotoxicity and active astrocytes via regulation of B-cell lymphoma-2 (Bcl-2), Bcl-2-like protein 4, and caspase-3 (Hou et al., 2017). Taken together, ginsenoside Rd has neuroprotective effects via mitogen-activated protein kinase (MAPK)/ERK-, PI3K/AKT, PI3K/AKT/GSK-3β, and ERK1/2-dependent pathways.

For inflammation, ginsenoside Rd inhibits ischemic stroke-induced neuronal death and inflammation by inhibiting cleaved poly adenosine diphosphate-ribose polymerase-1 (PARP-1) activity, levels of poly (ADP-ribose), sequential apoptosis-inducing factor (AIF) translocation, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) nuclear accumulation (Hu et al., 2013). Postischemic syntheses of two damaging enzymes, cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), are also significantly inhibited by ginsenoside Rd treatment. Ginsenoside Rd reduces free radical generation during I/R and suppresses oxidative damage and inflammatory injury (Ye et al., 2011d). As a proteasome-related compound, ginsenoside Rd protects against MCAO-induced ischemic brain injury by inhibiting the proteasome

**FIGURE 1** Biotransformation and pharmacokinetics of ginsenoside Rd in vivo.

- **Microbacterium trichothecenolyticum**
- **MAH-161**
- **β-glucosidase**
- **α-L-arabinosidase**
- **Ginsenoside CK**
- **Ginsenoside Rh2**
- **Ginsenoside Rb1**
- **Ginsenoside Rb2**
- **Ginsenoside Re**
- **β-glucosidase**

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activity and NF-κB/matrix metalloproteinase-9 (MMP-9) signal pathway (Zhang et al., 2020b). Ginsenoside Rd inhibits MCAO-induced microglial activation, decreases the expression levels of nuclear factor of kappa light polypeptide gene enhancer in B cell inhibitor, alpha (IkBa) phosphorylation and NF-κB nuclear translocation within a short time, and has fewer side effects than glucocorticoids (Zhang et al., 2016).

Other Nervous System Diseases

Ginsenoside Rd has a significant neuroprotective effect on a variety of neurological diseases, which may be related to its promotion of stem cell proliferation (Shi et al., 2005) and differentiation into astrocytes (Lin et al., 2012). Ginsenoside Rd may promote neurite outgrowth by upregulating growth-associated protein of 43 kDa (GAP-43) expression via ERK- and ARK-dependent signaling pathways in NGF-induced PC12 cells (Wu et al., 2016).

In H2O2-induced PC12 cells, ginsenoside Rd, as a neuroprotective agent, has neuroprotective effects on neurodegenerative diseases (Ye et al., 2008). In the converting monocyte phenotype and macrophages of the Guillain–Barre syndrome (GBS) mouse model, ginsenoside Rd attenuates experimental autoimmune neuritis (Ren et al., 2021). Ginsenoside Rd can regulate MMP by decreasing intracellular ROS and enhancing the activity of antioxidant enzymes and mitochondrial complex, thereby increasing intracellular ATP levels and ultimately reducing 1-methyl-4-phenylpyridinium (MPP+)-induced cell death in Parkinson’s disease (PD) (Liu et al., 2015b). Meanwhile, in the Aβ25–35-induced neuronal damage model, apoptosis and oxidative stress are ameliorated by ginsenoside Rd by regulating antioxidant capacity and the production of apoptotic proteins (Liu et al., 2015c). Learning and memory abilities can be improved in ginsenoside Rd-pretreated APP transgenic mice by significantly suppressing the NF-κB pathway to reduce the generation of proinflammatory factors (Liu et al., 2015d). Ginsenoside Rd-mediated neuroprotective effects against Alzheimer’s disease (AD) progression play a significant role in Neuro2a cells (Kim et al., 2014b). Ginsenoside Rd pretreatment can inhibit tau protein phosphorylation by maintaining a balance of GSK-3β, cyclin-dependent kinase 5 (CDK5/P25), and protein phosphatase 2A (PP-2A) (Li et al., 2011a; Li et al., 2021), respectively. Moreover, ginsenoside Rd increases the soluble amyloid-β precursor protein α (sAPPα) level and reduces extracellular Aβ to enhance the cognitive and memory functions of ovariectomy rats (Yan et al., 2017).

In experimental autoimmune encephalomyelitis, ginsenoside Rd exerts a neuroprotective role by regulating the immune response and inflammatory reaction via a signal pathway of IFN-γ/IL-4, BDNF/NGF (Zhu et al., 2014), and Foxp3/ROTy/RAS/STAT3 (Jin et al., 2020a). In spinal cord injury (SCI) models, ginsenoside Rd shows

![FIGURE 2 | Protective effect of ginsenoside Rd on ischemic stroke.](image-url)
anti-inflammatory effects consistent with dexamethasone that could significantly decrease the biomarkers of apoptosis, inflammation, oxidative damage factor, and repaired damaged mitochondria; particularly, there is no obvious difference in terms of dexamethasone in anti-inflammatory (Zhou et al., 2014; Cong and Chen, 2016), and these effects depended on the ASK1/JNK pathway (Wang et al., 2014). In the pathology of noise-induced hearing loss (NIHL), ginsenoside Rd could alleviate the apoptosis and oxidative stress damage on neuron cells by activating the SIRT1/PGC-1α signaling pathway (Chen et al., 2020). In addition, ginsenoside Rd treatment effectively eliminates the oxidative injury and the production of proinflammatory factors and peroxides in the chronic restraint stress (CRS) paradigm (Wang et al., 2020). Ginsenoside Rd pretreatment may be neuroprotective in old rats following acute Pb exposure through limited microglial activation and maintained neural stem cell proliferation (Wang et al., 2013a).

To summarize, ginsenoside Rd can play a significant role in neuron damage by inhibiting the production of excitatory amino acids, reducing the intracellular Ca2+ influx mediated by the NMDA pathway, changing the neurotoxicity of Ca2+ to mitochondrial function damage, and regulating apoptosis-inducing and neuroinflammatory factors (Table 2).

Cancer

As indicated in Table 3 and Figure 3, ginsenoside Rd can inhibit the proliferation of various cancer cells by participating in the apoptotic pathway. As a potential therapeutic and specific 26S proteasome inhibitor, ginsenoside Rd plays an important role in anticancer therapy by targeting 26S proteasome (Chang et al., 2008).

Table 2

| References | Diseases | Experimental model | Effects | Mechanism |
|-----------|----------|--------------------|---------|-----------|
| Tian et al. (2020) | Gastric cancer | MKN-45, SGC-7901 cells | Caspase-3, caspase-9↑, Cyclin D1↓ | Apoptosis |
| Kim et al. (2013b) | Gastric cancer | AGS cells | Caspase-3, caspase-8, PARP↑ | Apoptosis |
| Chian et al. (2019) | NSCLC | A549 NSCLC cells | Caspase-3↑, Bcl-2, hTERT↓ | Proliferation |
| Gu et al. (2019) | Glioblastoma | U251 cells | miR-144-5p, TLR2↑, Toll-like receptor 2↓, Smad2↑ | Apoptosis |
| Liu et al. (2020b) | Glioblastoma | U251 cells, H4 (HTB148), U87 MG cells | Bax, caspase-3, HIF-1α↑, Bcl-2↓ | Apoptosis |
| Phi et al. (2019) | Colorectal cancer | Human CRC cell, HT29 cells/SW620, NSG mice | MDR1↓ | Resistance |
| Zhang et al. (2017) | Breast cancer | HUVECs, MDA-MB-231 cells/Thymic nude mice | Bax↑, Bcl-2↓ | Apoptosis |
| Kim et al. (2013) | Breast cancer | AGS cells, MCF-7 cells | Caspase-3↑, Smad2↑, miR-18a↓ | Apoptosis |
| Wang et al. (2016) | Breast cancer | 4T1 cells, MDA-MB-231 cells/Female BALB/c mice | Caspase-3↑, miR-18a↑, SMAD2↑ | Attenuates metastasis |
| Pokharel et al. (2013) | Breast cancer | MCF-7/ADR cells | MDR1↓ | Resistance |
| Yang et al. (2006b) | Cervical cancer | HeLa cells | Bax↑, Bcl-2↓ | Apoptosis |
| Yang et al. (2021a) | Hepatocellular carcinoma | HepG2 cells/Male BALB/c nude mice | MMP-1↑, MMP-2↑, MMP-7↓ | Proliferation, apoptosis |
| Yoon et al. (2012) | Hepatocellular carcinoma | HepG2 cells | Blocking MAPK signaling and inducing the formation of focal adhesions |

Table 3

| References | Diseases | Experimental model | Effects | Mechanism |
|-----------|----------|--------------------|---------|-----------|
| Tian et al. (2020) | Gastric cancer | MKN-45, SGC-7901 cells | Caspase-3, caspase-9↑, Cyclin D1↓ | Apoptosis |
| Kim et al. (2013b) | Gastric cancer | AGS cells | Caspase-3, caspase-8, PARP↑ | Apoptosis |
| Chian et al. (2019) | NSCLC | A549 NSCLC cells | Caspase-3↑, Bcl-2, hTERT↓ | Proliferation |
| Gu et al. (2019) | Glioblastoma | U251 cells | miR-144-5p, TLR2↑, Toll-like receptor 2↓, Smad2↑ | Apoptosis |
| Liu et al. (2020b) | Glioblastoma | U251 cells, H4 (HTB148), U87 MG cells | Bax, caspase-3, HIF-1α↑, Bcl-2↓ | Apoptosis |
| Phi et al. (2019) | Colorectal cancer | Human CRC cell, HT29 cells/SW620, NSG mice | MDR1↓ | Resistance |
| Zhang et al. (2017) | Breast cancer | HUVECs, MDA-MB-231 cells/Thymic nude mice | Bax↑, Bcl-2↓ | Apoptosis |
| Kim et al. (2013) | Breast cancer | AGS cells, MCF-7 cells | Caspase-3↑, Smad2↑, miR-18a↓ | Apoptosis |
| Wang et al. (2016) | Breast cancer | 4T1 cells, MDA-MB-231 cells/Female BALB/c mice | Caspase-3↑, miR-18a↑, SMAD2↑ | Attenuates metastasis |
| Pokharel et al. (2013) | Breast cancer | MCF-7/ADR cells | MDR1↓ | Resistance |
| Yang et al. (2006b) | Cervical cancer | HeLa cells | Bax↑, Bcl-2↓ | Apoptosis |
| Yang et al. (2021a) | Hepatocellular carcinoma | HepG2 cells/Male BALB/c nude mice | MMP-1↑, MMP-2↑, MMP-7↓ | Proliferation, apoptosis |
| Yoon et al. (2012) | Hepatocellular carcinoma | HepG2 cells | Blocking MAPK signaling and inducing the formation of focal adhesions |
MCF-7 cells by enhancing caspase-3 activity, mitochondrial depolarization, and sub-G1 populations (Kim, 2013). In 4T1 cells, the expression of Mir-18a and Smad2 decreases with ginsenoside Rd treatment (Wang et al., 2016). Furthermore, ginsenoside Rd promotes the ubiquitination of MDR1 and inhibits doxorubicin resistance in MCF-7/ADR cells (Pokharel et al., 2010). In cervical cancer, ginsenoside Rd treatment in HeLa cells upregulates Bax expression, downregulates Bcl-2 expression, decreases the mitochondrial transmembrane potential, activates the caspase-3 pathway, significantly inhibits proliferation, and induces apoptosis (Yang et al., 2006b).

Finally, in HepG2 cells and the HepG2 cell-injected nude mice-induced hepatocellular carcinoma model, the combination of CA4P and ginsenoside Rd has synergistic antitumor effects via the PI3K/AKT/mTOR signaling pathway-related inhibition of HIF-1α (Yang et al., 2021a). HepG2 cells treated with ginsenoside Rd noticeably promoted matrix metalloproteinases’ (MMPs) activation, and MAPK signaling pathways were involved in cancer cell migration, thereby suggesting that ginsenoside Rd inhibits the activity of HepG2 cells in a dose-dependent and time-dependent manner (Yoon et al., 2012).

**Gastric and Gut**

In a sodium dextran sulfate (DSS)-induced colitis model, ginsenoside Rd reduces DSS-induced colonic pathology via the adenosine 5′-monophosphate-activated protein kinase/AMPK-activated autophagy signaling pathway and the inhibition of the production of proinflammatory cytokines (IL-1β, TNF-α, and IL-6) in serum and colon tissues (Liu et al., 2018). In irradiation-induced intestinal epithelial cells, ginsenoside Rd reduces apoptosis by activating a pathway of PI3K/AKT, inactivates MEK, and inhibits a mitochondria/caspase pathway (Tamura et al., 2008). Meanwhile, in 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced ulcerative colitis model, ginsenoside Rd showed obvious anti-inflammatory activity by inhibiting neutrophil infiltration, regulating apoptosis signal and oxidative stress (Yang et al., 2012a), reduced the accumulation of leukocytes, and downregulated multiple proinflammatory cytokines (Yang et al., 2012b).

**Metabolic Diseases**

Laboratory data of ginsenoside Rd suggest that it has effects on multiple metabolic diseases. The browning of white adipose tissue
induced by cold stress and cAMP levels are increased by ginsenoside Rd. In particular, Rd alleviates obesity and insulin resistance by upregulating thermogenesis through the cAMP/protein kinase A (PKA) signaling pathway (Yao et al., 2020). In fast-food diet-induced non-alcoholic fatty liver disease (NAFLD), fermented ginsenoside Rd with Cordyceps militaris regulates lipid metabolism and the inflammatory response via mTORC1 signaling (Choi et al., 2019). Ginsenoside Rd inhibits the progress of the death of islet transplantation by decreasing the apoptosis of the islet cells (Kaviani et al., 2019). In the atherosclerosis process, ginsenoside Rd decreases oxidized low-density lipoprotein (Ox-LDL) and cholesterol by inhibiting Ca<sup>2+</sup> influx (Li et al., 2011b). In diabetic db/db mice and mesangial cells, pectin-lyase-modified ginsenoside Rd relieves diabetic nephropathy via alleviated ROS production (Jung et al., 2021).

**Other Diseases**

Ginsenoside Rd has positive effects on skin injury, osteoporosis, kidney injury, vessel injury, heart injury, lung injury, aging, and inflammation. In animal wound models, ginsenoside Rd significantly increases wound healing by promoting the proliferation and migration level of keratinocyte progenitor cells (KPCs) and human dermal fibroblasts (HDFs) (Kim et al., 2013c). Ginsenoside Rd also has a positive effect on rejection caused by a transplant skin allograft (Wang et al., 2012a). Beyond that, ginsenoside Rd, as an antiosteoporotic agent, promotes differentiation and mineralization in osteoblastic MC3T3-E1 cells (Kim et al., 2012). In animal models of renal I/R injury and cultured proximal tubule cells, ginsenoside Rd has a protective effect by inhibiting inflammation and regulating biochemical indexes of renal function (Yokozawa et al., 1998; Ren et al., 2016). In addition, ginsenoside Rd downregulates NF-kB and the expression of iNOS and COX-2 in lipopolysaccharide (LPS)-induced Institute of Cancer Research (ICR) mice, and RAW264.7 cells were suppressed (Kim et al., 2013d). In the nicotine-induced vascular endothelial injury model, ginsenoside Rd plays an important role in the prevention of cardiovascular diseases via participation in NO signaling and regulates platelet and vascular function (Zhang et al., 2020c). Ginsenoside Rd upregulates Cyto C release and caspase-9/caspase-3 activation and decreases the MMP and the ratio of Bcl-2/Bax via the mitochondria-dependent pathway in H<sub>2</sub>O<sub>2</sub>-induced apoptosis in basilar artery smooth muscle cells (BASMCs) (Li et al., 2012). Furthermore, ginsenoside Rd could relieve the cisplatin-induced kidney injury (Yokozawa and Liu, 2000; Yokozawa and Dong, 2001) and kidney proximal tubules cephalexin injury under cephalexin treatment (Yokozawa and Dong, 2001). In an adenocorticotrophic hormone (ACTH)-induced corticosterone secretion cell model, ginsenoside Rd inhibits ACTH-induced corticosterone production by inhibiting the MC2R-cAMP/PKA/cyclic AMP response element binding (CREB) pathway in adrenocortical cells (Jin et al., 2020b). In myocardial I/R-induced rats and simulated I/R-induced primary neonatal rat cardiomyocyte models, ginsenoside Rd promotes cardioprotection via the activation of Akt/GSK-3β signaling (Wang et al., 2013b). In addition, ginsenoside Rd can protect against LPS-induced acute lung injury by inhibiting the PI3K/AKT signaling pathway (Yang et al., 2021b). Other studies have indicated that ginsenoside Rd can significantly enhance the survival time of Caenorhabditis elegans via lipid metabolism and the activation of the stress response signaling pathway (Yu et al., 2021) and can alleviate the oxidative damage caused by aging in senescence-accelerated mice (Yokozawa et al., 2004). Finally, the anti-inflammatory activity of ginsenoside Rd is well documented, is considered to be associated with its antioxidant effects (Kim et al., 2007; Zhang et al., 2013b), and selectively produces prostaglandin E2 (PGE2) by activating the CCAAT/enhancer binding protein (C/EBP) and CREB to express COX-2 (Jeong et al., 2007). Ginsenoside Rd exerts anti-inflammatory effects in carrageenan-induced inflammation rats via the inhibition of the NF-κB signaling pathway (Wang et al., 2012b) and in ovalbumin-induced allergic rhinitis mice by regulating multiple inflammatory factors (Kim et al., 2019) and elicits a Th1 and Th2 immune responses (Yang et al., 2007b). Ginsenoside Rd enhances the Th1 response to surface mannan extract in mice, which protects mice from disseminated candida infection by stimulating higher titers of Th1 antibodies and a Th1-dominated immune response (Han and Rhew, 2013).

**CONCLUSION AND PERSPECTIVE**

As a widely used herbal medicine, ginseng appears in the form of dietary supplements nowadays. Available evidence suggests that the antiapoptotic, antioxidant, and anti-inflammatory activities, which suppress the calcium influx of ginsenoside Rd, may have an important role in the neuroprotective and anticancer effects. Ginsenoside Rd play a crucial role in neuroprotective, anticancer effects, metabolism, and other diseases by regulating PI3K/AKT, inhibiting Cyto C released and caspase activation, and regulating the release of inflammatory factors, which play a crucial role in neuroprotective, anticancer effects, metabolism, and other diseases.

In addition, ginsenoside Rd has potential therapeutic effects on regulating metabolism and in multigorgan protection. However, attributable to the shortage of clinical studies on ginsenoside Rd, it is difficult to make a clear decision. In addition to exploring its various activities, it is suggested to verify existing activities in a deeper mechanism, design clinical trials to prove its safety and effectiveness, and obtain a more extensive clinical application.

**AUTHOR CONTRIBUTIONS**

JnL, QH, and YY collected, analyzed, and reviewed the literature and wrote the main manuscript; PJ, JC, ME, ZZ, HQ, JaL, and ZC added/checked references and assembled figures/tables; DZ and LZ revised the manuscript; and XL and LZ designed and supervised the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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GLOSSARY

PPD protopanaxadiol
LC-MS liquid chromatography-mass spectrometry
MCAO middle cerebral artery occlusion
GLT-1 glutamate transporter-1
NMDA N-methyl-D-aspartate
NR2B N-methyl-D-aspartate receptor 2B
OGD oxygen–glucose deprivation
TRPM transient receptor potential melastatin
ASIC acid-sensing ion channel
MMP mitochondrial membrane potential
ROS reactive oxygen species
SD Sprague–Dawley
mtDNA mitochondrial DNA
nDNA nuclear DNA
PKB protein kinase B
GSK-3β glycogen synthase kinase-3β
PKB protein kinase B
OGD/R oxygen–glucose deprivation/reperfusion
I/R ischemia/reperfusion
VEGF vascular endothelial growth factor
BDNF brain-derived neurotrophic factor
PI3K phosphatidylinositol 3-kinase
TMT trimethyltin
Bcl-2 B-cell lymphoma-2
MAPK mitogen-activated protein kinase
PARP-1 poly adenosine diphosphate-ribose polymerase-1
AIF apoptosis-inducing factor
NF-κB nuclear factor kappa-light-chain-enhancer of activated B cells
COX-2 cyclooxygenase-2
iNOS inducible nitric oxide synthase
MMP-9 matrix metalloproteinase-9
IkBα nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha
GAP-43 growth-associated protein of 43 kDa

GBS Guillain–Barre syndrome
MPP+ 1-methyl-4-phenylpyridinium
PD Parkinson’s disease
AD Alzheimer’s disease
CDK5/P25 cyclin dependent Kinase 5
PP-2A protein phosphatase 2A
sAPPα soluble amyloid-β precursor protein α
SCI spinal cord injury
NIHL noise-induced hearing loss
CRS chronic restraint stress
NSCLC non-small-cell lung cancer
NRF2 nuclear factor erythroid 2-associated factor 2
DDP cisplatin
EGFR epidermal growth factor receptor
mTOR mammalian target of rapamycin
HIF1-α hypoxia-inducible factor 1-α
MMPs matrix metalloproteinases
DSS sodium dextran sulfate
AMPK adenosine 5’-monophosphate-activated protein kinase
ULK1 Unc-51 like autophagy activating kinase 1
TNBS trinitrobenzenesulfonic acid
PKA protein kinase A
NAFLD non-alcoholic fatty liver disease
Ox-LDL oxidation low lipoprotein
KPCs keratinocyte progenitor cells
HDFs human dermal fibroblasts
LPS lipopolysaccharides
ICR Institute of Cancer Research
BASMCs basilar artery smooth muscle cells
ACTH adrenocorticotropic hormone
PGE2 prostaglandin E2
C/EBP CCAAT/enhancer binding protein
CREB cyclic AMP response element binding protein