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Review Article

Effects of Red ginseng on neuroinflammation in neurodegenerative diseases

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ABSTRACT

Red ginseng (RG) is widely used as a herbal medicine. As the human lifespan has increased, numerous diseases have developed, and RG has also been used to treat various diseases. Neurodegenerative diseases are major problems that modern people face through their lives. Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis are featured by progressive nerve system damage. Recently, neuroinflammation has emerged as a degenerative factor and is an immune response in which cytokines with nerve cells that constitute the nervous system. RG, a natural herbal medicine with fewer side effects than chemically synthesized drugs, is currently in the spotlight. Therefore, we reviewed studies reporting the roles of RG in treating neuroinflammation and neurodegenerative diseases and found that RG might help alleviate neurodegenerative diseases by regulating neuroinflammation.

1. Introduction

Inflammation is a defensive response to harmful stimuli [1]. The inflammatory response is an immune response that occurs when immune cells and various cytokines interact with each other during signaling [2–4]. Inflammation is a reaction that occurs in all tissues and various parts of the body, such as the brain, joints, and cancer [5–7].

As life expectancy increases, the number of patients with neuroinflammatory conditions, such as neurodegenerative diseases also increases [8,9]. Neuroinflammation is an inflammatory response that occurs in the nerve tissue; is chronic and caused by stress, addictive drugs, viruses, and aging [10–13]; and causes nerve damage in neurodegenerative diseases, neuroimmune diseases, and drug addiction, leading to symptoms such as oxidative stress, further drug addiction, and cognitive disorders [14–16]. Thus, many types of anti-inflammatory drugs, such as minocycline, naproxen, and ibuprofen, have been developed and used [17,18]. For example, ibuprofen is a nonsteroidal anti-inflammatory drug, which decreases neuroinflammation in newborn animal models with restricted growth [19]. In humans, ibuprofen has been used to treat Alzheimer's disease (AD). However, its use remains controversial because the side effects of ibuprofen outweigh its benefits [20]. Similarly, currently available anti-inflammatory drugs have various side effects such as gastric ulcer, myocardial infarction, renal damage, and hepatotoxicity [21–23]. In order to address these challenges, presently, there is an increasing inclination towards exploring novel anti-inflammatory agents derived from natural or herbal sources, which generally exhibit fewer adverse effects compared to the presently accessible anti-inflammatory drugs [24,25].

Ginseng is divided into *Panax ginseng Meyer* (*P. ginseng*), *Eleutherococcus senticosus*, and *Panax quinquefolius*, but all belong to the family Araliaceae [26]. *P. ginseng* is a traditional medicinal herb that has been widely used in Korea, China, Japan, and other Asian countries and has been extensively studied and used as a natural herbal medicine.

Red ginseng (RG) is processed from *P. ginseng* by steaming and drying the roots [27]. Ginsenosides, the components of ginseng and RG have been shown to have anti-inflammatory, antioxidant, and motor function improvement in various diseases [28–30]. Ginsenosides are divided into three groups according to their chemical structure: panaxadiol, panaxatriol, and oleanolic acid [31–33]; panaxadiol: Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1, Rg5, panaxatriol: Re, Rf, Rg1, Rg2, Rh1, and oleanolic acid: Ro (Figs. 1–3). Especially, ginsenoside Rg3 and Rg5 are a unique RG component [34]. It was

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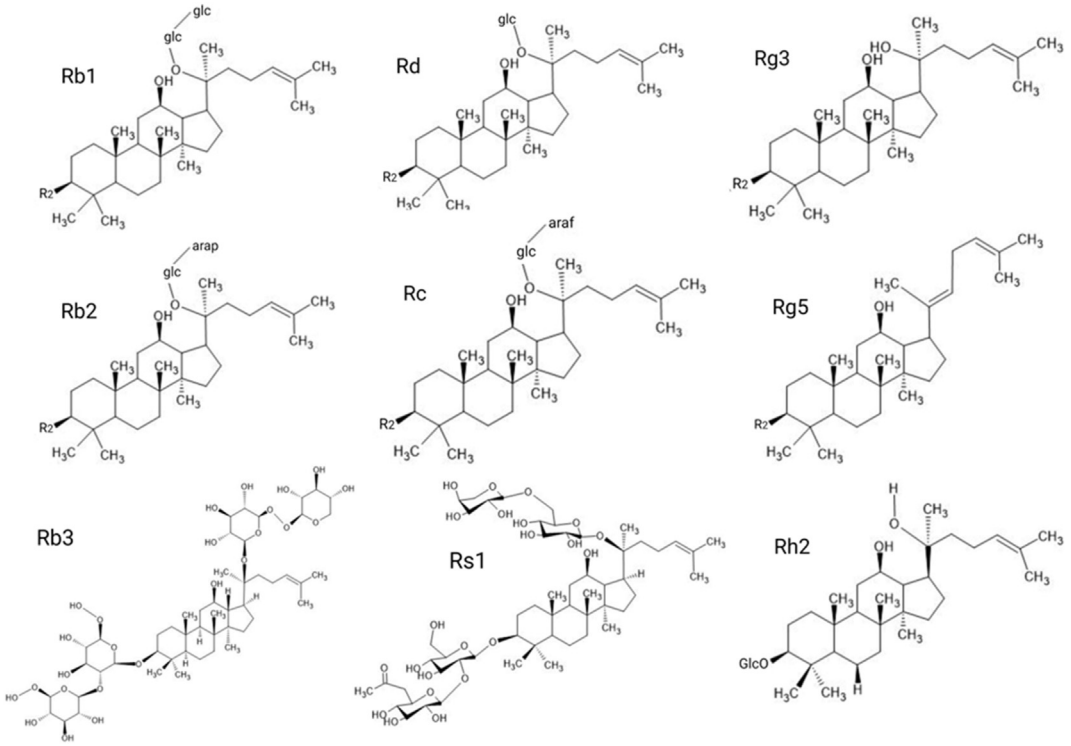

Fig. 1. Ginsenoside Panaxadiol
The chemical structures of ginsenoside panaxadiol components (Rb1, Rb2, Rb3, Rc, Rd, Rg3, Rh2, Rs1, Rg5) are shown
glc: β-D-glucopyranosyl, R2: glc-glc-O, arap: α-L-arabinopyranosyl, araf: α-L-arabinofuranosyl, GlcO: glc-O.

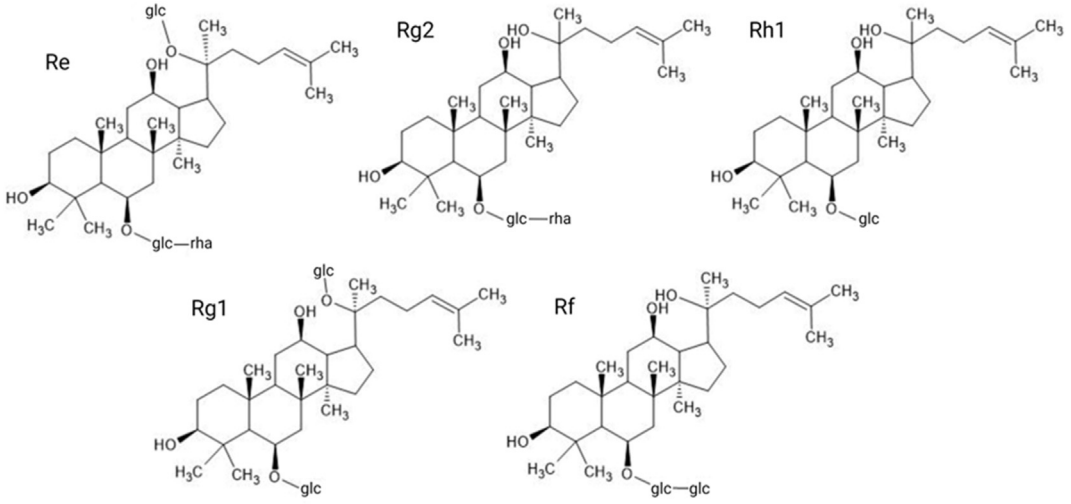

Fig. 2. Ginsenoside Panaxatriol
Indicate the chemical structure of Ginsenoside (Re, Rf, Rg1, Rg2, Rh1).
glc: β-D-glucopyranosyl, R2: glc-glc-O, rha, α-L-rhamncpyranosyl

made by changing the chemical structures of Rb1, Rb2, Rc and Rd in the process of steaming (Fig. 4). Additionally, Rg5 is a ginsenoside component derived from the modification of the chemical structure of Rg3, and both belong to the panaxadiol family [35].

RG has anti-inflammatory effects in neurodegenerative diseases such as AD, Parkinson's disease (PD), and Huntington's disease (HD) [36–38]. RG alleviated the symptoms of neurodegenerative disease by regulating neuroinflammatory pathways such as the mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathways and decreasing inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2), and nitric oxide (NO).

However, the exact mechanism through which RG relieves inflammation remains still unclear. Thus, the purpose of this study was to investigate the effects of RG on the inflammatory response in neurodegenerative diseases to understand the potential mechanisms of RG in reducing neuroinflammation.

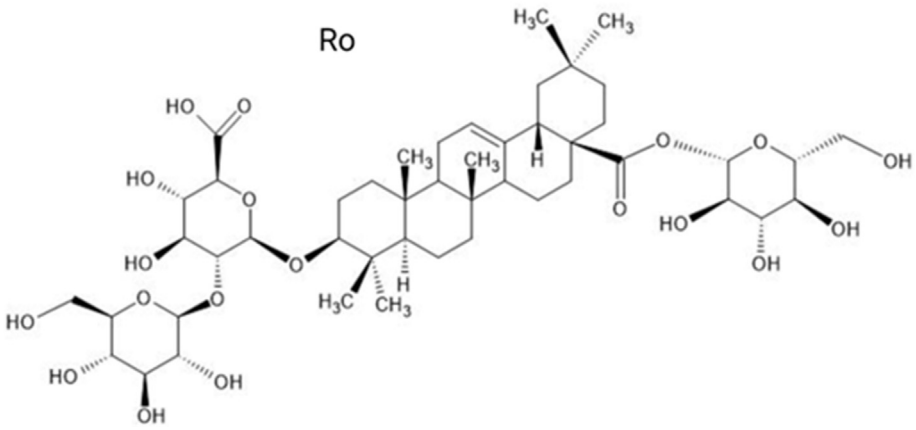

Fig. 3. Ginsenoside Oleanolic acid
The figure shows the chemical structure of the ginsenoside oleanolic acid component (Ro).

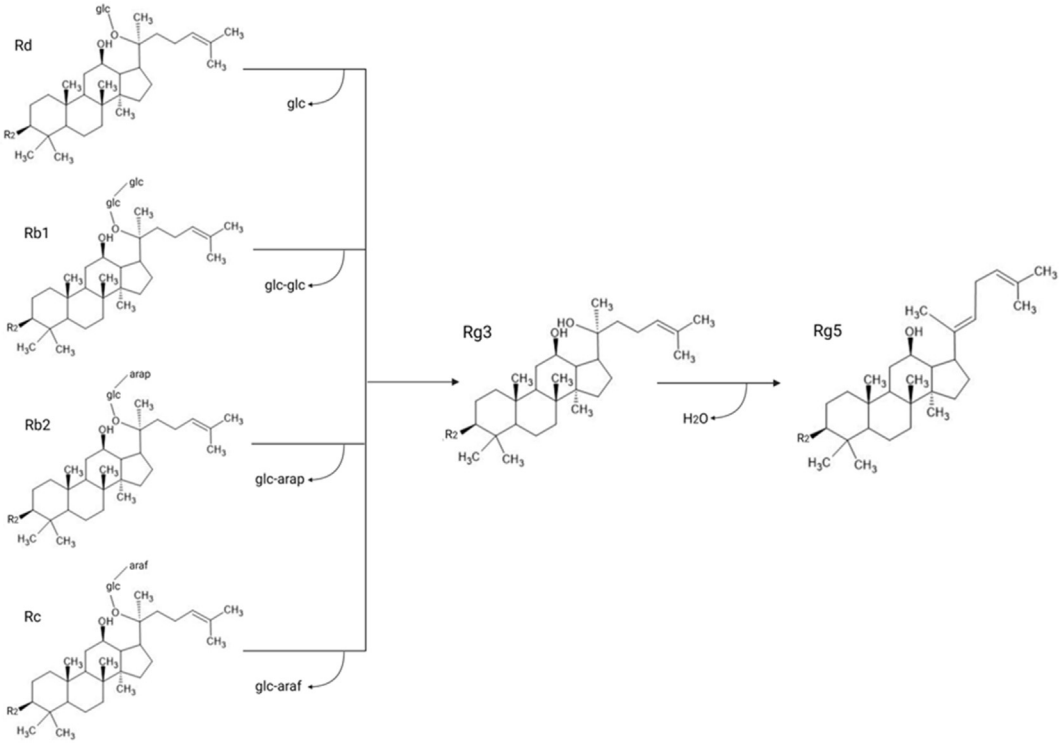

Fig. 4. Changes in the chemical structure of ginsenoside during steaming
The figure shows the process in which Rg3 and Rg5, unique compounds of red ginseng, are produced during the steaming process. The chemical structure of Ginsenoside Rb1, Rb2, Rc, and Rd is converted to Rg3, and Rg3 to Rg5.
glc: β-D-glucopyranosyl, R2: glc-glc-O, arap: α-L-arabinopyranosyl, araf: α-L-arabinofuranosyl.

2. Effects of RG on neurodegenerative diseases

Neurodegenerative diseases are in which the neurons of the central nervous system are structurally and functionally lost, resulting in slow and progressive disorders such as AD, PD, HD, and amyotrophic lateral sclerosis (ALS) [39]. The major feature of neurodegenerative diseases is the neuroinflammatory response, which is significantly involved in the process of neurodegeneration [40].

2.1. Alzheimer's disease

AD is a neurodegenerative disease characterized by gradual loss of brain cells with age and is the most common form of dementia. In AD, proteins such as amyloid-β(Aβ) and tau accumulate in the brain and cause neuroinflammation, which leads to impaired of learning and memory, and motor function disorders [41–44].

Aβ accumulation is caused by the inappropriate cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase,

resulting in Aβ aggregation and the formation of oligomers and plaques. Aβ causes neurotoxicity, releases cytokines, and aggravates AD by inducing an inflammatory response [45]. RG alleviates neuroinflammation induced by Aβ. For example, ginsenoside Rg5 attenuated neuroinflammatory effects by inhibiting TNF-α and IL-1β and decreasing Aβ deposition in STZ-induced memory-impaired rats [46]. Additionally, Rg5 increased brain-derived neurotrophic factor (BDNF) expression, thereby reducing cognitive deficits. RG oil (RGO) modulates the MAPK/NF-κB pathway to alleviate Aβ 25−35-induced neuronal apoptosis, oxidative stress, and inflammation [47]. In addition, RGO alleviated neuroinflammation by diminishing the expression of TNF-α, inducible Nitric Oxygen Synthase (iNOS), and COX-2 and inhibited the MAPK and NF-κB pathways in PC12 cells stimulated with Aβ 25−35 [37]. Aβ affects microglia, the immune cells in the brain responsible for various immune functions. In AD, Aβ plaques activate microglia, making them hyperreactive to immune responses and phagocytosis, which, as a result, becomes the main cause of neuroinflammation [48]. Microglia are activated via the NF-κB pathway. Aβ deposition activates microglia and consequently releases inflammatory cytokines. Secreted inflammatory cytokines such as TNF-α, IL-6, and IL-1β increased APP and Aβ production and these cytokines finally lead to extended neuroinflammation [49]. RG, ginseng total saponins (GTS), and ginsenoside Rg3 suppressed IL-1β, IL-6, TNF-α, and iNOS mRNA expression, alleviating neuroinflammation caused by microglial activation, suggesting that RG is a natural drug that strongly inhibits microglial activation [50,51]. Furthermore, ginsenoside Rh1 inhibits the transcription of MAPK and NF-κB in microglia and increases the expression of IL-10 that an anti-inflammatory cytokine [28]. Therefore, Jung et al reported that RG plays a positive role in the anti-inflammatory mechanism by modulating both inflammatory and anti-inflammatory cytokines. In addition, ginsenoside Rb1 and Rh2 suppress the inflammatory cytokines IL-6, IL-1β, and TNF-α in the activation of microglial cells by LPS-induced neuroinflammation, thereby showing anti-inflammatory effects and alleviating neuroinflammation [52,53]. Non-saponin components from RG such as Gintonin and Non-saponin fraction with rich polysaccharide (NFP) also exerted an anti-neuroinflammatory effect [54,55]. Gintonin is a glycolipoprotein that is a non-saponin component of RG [54]. Gintonin suppressed the expression of TNF-α and p-NFκB in microglia and astroglia and alleviated Aβ-stimulated neuroinflammation. Moreover, gintonin reduced amyloidogenic factors, and improved synaptic dysfunction and cognitive impairment, proving that gintonin can be utilized for AD treatment. NFP is an acidic polysaccharide and a fraction of the RG [55]. Treatment of the NFP in the AD animal model showed ionized calcium-binding adapter molecule 1 (Iba-1) of microglia inflammatory maker significantly decreased. In addition, NFP stimulated neurogenesis in the hippocampus and inhibited Aβ induced neuronal cell death.

APP is a membrane protein and a precursor of Aβ. A relationship between APP and neuroinflammation has been reported to exist. APP induces neuroinflammation and, reduces neurogenesis in mouse hippocampi [56]. Inflammatory cytokines TNF-α, IL-1β, and interferon- γ (IFN-γ) secreted during neuroinflammation increase the expression of APP [57,58]. Moreover, RG components influenced the cognitive abilities and neuroinflammation in APP transgenic (Tg) mice. For example, ginsenoside Rd not only improves cognitive abilities but also exhibits neuroprotective effects in APP Tg mice [59]. Rd inhibits the activation of the NF-κB pathway, reduces the expression of pro-inflammatory cytokines IL-1β, IL-6 IL-8, and TNF-α, and increases the expression of IL-10. In addition, ginsenoside Rg1 alleviated nerve damage by reducing APP expression and Aβ deposition in APP/PS1 mice [60].

Tau is a protein microtubule-associated proteins that maintains axonal microtubule assembly and stability [61]. However, in AD tau aggregates into a pair of helical filaments and fails to maintain microtubules. Excessive phosphorylation and misfolding of the tau protein induce pathological phenomena such as neurofibrillary tangles, which eventually lead to neuroinflammatory responses [61,62]. Tau pathology and neuroinflammation of the para-hippocampus are directly linked with the pathology of early-stage Alzheimer's patients [63]. Studies have shown the risk of tau in humans and AD-related Tg mouse models. Increased tau expression is associated with an increase in the neuroinflammatory response and a decrease in cognitive abilities in various AD animal models such as 5XFAD, P301S tau Tg, and Ala152Thr-Tau Tg mice [64−66].

RG relieves the detrimental effects of tau-induced neuroinflammation in AD. RG inhibits tau aggregation and promotes degradation by reducing tau phosphorylation in the hippocampus and cortex [67]. Furthermore, ginsenoside Rg1 reduces tau phosphorylation and modulates the maintaining cellular homeostasis signaling pathway, the Wnt/GSK-3β/β-catenin pathway, to reduce oxidative stress, apoptosis, and neuroinflammation [29]. Other studies have shown that ginsenoside repaired hippocampal damage and reduction of the expression of p-tau in d-galactose- and AlCl3-induced AD models [68]. Additionally, hyperphosphorylated tau activates the NF-κB pathway [69], and ginsenosides Rd and Rb1 reduce tau hyperphosphorylation, protecting neurons and reducing neuroinflammation [70,71].

Several cytokines are involved in tau hyperphosphorylation. IL-6, an inflammatory cytokine, promotes hyperphosphorylation of tau, whereas IL-10, an anti-inflammatory cytokine, inhibits abnormal phosphorylation of tau [72]. When IL-10 is deficient, inflammatory cytokines such as IL-6, IL-1β, IL-12, and TNF-α are generated, which promote hyperphosphorylation of tau. RG modulates the expression of various cytokines and affects tau phosphorylation to exert positive effects on neuroinflammation. Particularly, ginsenoside Rb1 inhibits the phosphorylation of tau induced by Aβ25-35 and reduces the mRNA expression of TNF-α and iNOS [71,73]. RG attenuates neuroinflammation in AD by inhibiting tau phosphorylation and inflammatory cytokine levels. In addition, RG regulates the neuroinflammatory pathway via tau phosphorylation through an anti-inflammatory mechanism by increasing the expression of IL-10. Ginsenoside Rb1 upregulates IL-10 levels in the hippocampus to alleviate neuroinflammation, and ginsenoside Rd reduces tau phosphorylation to exert anti-inflammatory and neuroprotective effects [70,74]

Therefore, these studies suggests that RG is a natural herb-drug mitigates AD by dissolving the aggregation of Aβ and tau protein, which are emerging as the main causes of AD, and ameliorating the resulting inflammation (Fig. 5).

2.2. Parkinson's disease

PD occurs primarily during senescence and is the second most common neurodegenerative disease after AD. PD causes motor dysfunction due to the loss of dopamine (DA) neurons and misfolding and accumulation of α-synuclein (α-syn). PD occurs when DA neurons in the substantia nigra par compacta (SNpc), which form the DA pathway, are lost or die. Symptoms include tremors, slow movements, stiffness, and motor dysfunction such as stooped and unstable postures. PD triggers symptoms such as neuroinflammation, autonomic dysfunction, depression, cognitive decline, dementia, and motor dysfunction [75,76].

Neuroinflammation in PD is induced by increased inflammatory factors, activation of NF-κB, and activation of microglia [77,78].

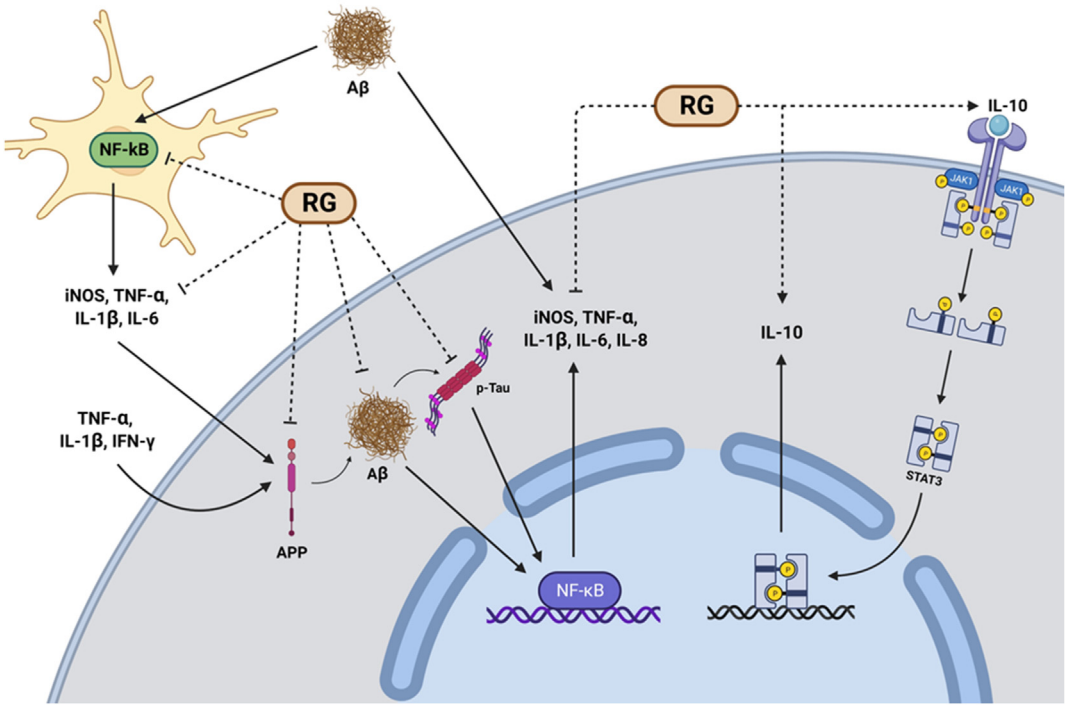

Fig. 5. Effects of Red ginseng on neuroinflammation in Alzheimer's disease
Red ginseng suppresses the expression of inflammatory cytokines by inhibiting NF-κB transcription in microglia activation and reducing amyloid precursor protein, amyloid-β, and the phosphorylation of Tau protein. In contrast, red ginseng exerts an anti-neuroinflammatory effect by increasing anti-inflammatory cytokines secretion.

Neuroinflammation causes degeneration and death of DA neurons and negatively affects the pathogenesis of PD [79].

RG exerted the effect of alleviating the neuronal inflammation that causes the loss of DA neurons. For example, RG, gintonin, and ginsenoside Rb1 suppressed MAPK and NF-κB pathways and declined IL-6, TNF-α, and COX-2 and activation of microglia in PD animal models [80–83]. Zaafan et al also reported that RG reduced oxidative stress, apoptosis, and other factors involved in neuroinflammation [82]. Rb1 enhances the levels of DA neurotransmitters in the SNpc and attenuates DA neuronal damage [83]. Ginsenoside Rg1 exerts anti-inflammatory and neuroprotective effects, and alleviates PD symptoms [38,84]. Through the activation of glutamate receptor (GR) and the inhibition of NF-κB and MAPK pathways, Rg1 demonstrates anti-inflammatory effects by suppressing the nuclear transcription of NF-κB and the polarization of M1 microglia. Rg1 reduced the activation of glial cells and the inflammatory factors IL-6, TNF-α, IL-1β, and NO. In addition, Rg1 improved DA neuron loss and behavior defects and shows a neuroprotective effect by increasing the survival of tyrosine hydroxylase (TH) neurons. Therefore, we suggest that RG and its components help relieve PD by mitigating neuroinflammation, improving behavioral disorders, and protecting DA neurons.

Furthermore, ginsenoside Rd and Re protect dopaminergic neurons from carbon tetrachloride (CCl4)-mediated neurotoxicity and exert anti-inflammatory effects in dopaminergic neurons by regulating inflammatory responses by reducing NO [85]. In particular, Rd shows an anti-neuroinflammatory effect in dopaminergic cells by preventing iNOS and COX-2 expression and reduces NO formation, and Prostaglandin E2 (PGE2) synthesis [86]. Moreover, ginsenoside Rg1 has a neuroprotective effect; it protects TH-positive cells of SNpc from MPTP toxicity and modulates the neuroinflammatory response by increasing CD3+ CD4+ T cells, CD3+ CD8+ T cells, CD4+ CD25+ Foxp3+ regulatory T cells and decreasing IL-1β, IL-6, TNF-α, and IFN-γ [87]. In addition, RG attenuates MPTP-destroyed dopaminergic neurons in the substantia nigra (SN) and striatum and prevents activation of microglia by downregulating IL-1β and TNF-α mRNA [88].

α-syn is a soluble protein present in presynaptic terminals of DA neurons and is induced by abnormal dopamine metabolism, NO, and inflammatory cytokines. α-syn induces neurotoxicity and neuroinflammation in SNpc. These α-syn dysfunctions are hallmarks of PD [89,90]. RG alleviates the symptoms of PD, such as α-syn-induced neuroinflammation, toxicity, and motor dysfunction. Ginsenoside Rg1, gintonin, and RG reduce the release of TNF-α and IL-1β by inhibiting the formation and aggregation of α-syn in SNpc of MPTP-induced PD animal model [30,88,91]. Particularly, Rg1 improves motor coordination and the loss of dopamine neurons, which are common features of PD [30]. Therefore, RG and some components alleviated α-syn-mediated neuroinflammation and have a neuroprotective effect in DA neurons of SNpc [30,88,91]. In addition, ginsenoside Rb1 degrades pre-formed α-syn fibrils and strongly suppresses α-syn fibrillation and toxicity [92].

Taken together, RG may play an important role in protecting dopaminergic neurons by preventing the accumulation of a-syn and modulating neuroinflammation. Thus, further studies are needed to confirm that RG is an effective natural herbal agent for the to mitigation of PD (Fig. 6).

2.3. Huntington's disease

HD is a fatal neurodegenerative disease accompanied by abnormal involuntary movement disorder, psychiatric and cognitive disorders, and dementia owing to mutation and aggregation of the huntingtin (HTT) protein [93]. HD is an autosomal dominant genetic disease caused by an abnormal repeat in the CAG sequence of the HTT, which that encodes the HTT protein, on the short arm of chromosome 4. The CAG sequence of the HTT gene is a codon for glutamic acid, which develops into HD when repeated 36-40 times or more; the longer the CAG sequence repeats, the faster the onset of HD. The most prominent symptom of HD is choreatic movements

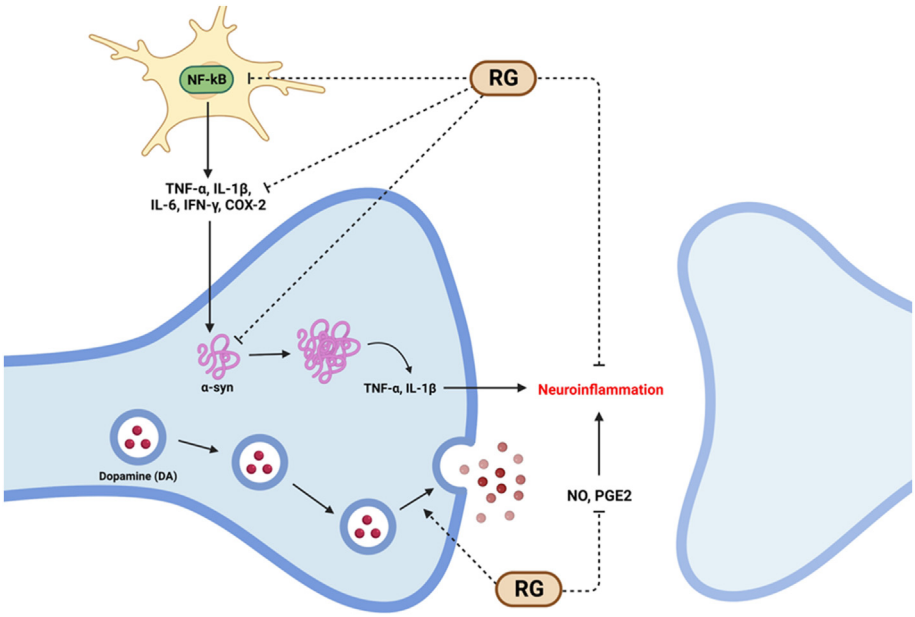

Fig. 6. Effects of Red ginseng on neuroinflammation in Parkinson's disease
Red ginseng inhibits NF-κB activation of microglia and prevents α-synuclein formation and aggregation, thereby lowering cytokines levels. Moreover, Red ginseng exerts an anti-inflammatory effect by decreasing nitric oxide and prostaglandin E2 levels, promoting dopamine release, and protecting dopaminergic neurons.

caused by muscle tension and stiffness. Other symptoms include psychiatric disorders, accompanied by depression, anxiety, and dementia caused by cognitive decline.

Neuroinflammation is closely associated with the pathogenesis of HD. LPS-induced neuroinflammation increases the levels of inflammatory cytokines, IL-6, IL-1β, and TNF-α, and abnormal activation of NF-κB in the postmortem brains of HD patients and the brains of HD animal models [94]. The expression of mutant HTT (mHTT) also activates the NF-κB pathway and is involved in neuroinflammation in HD.

RG and ginsenoside Rg1 exert therapeutic and neuroprotective effects by attenuating neuroinflammation and improving the symptoms of 3-nitro propionic acid (3-NP) induced HD in an animal model [36,95]. RG and Rg1 diminish the level of production of iNOS, TNF-α, IL-6, and IL-1β and suppress striatal microglial activation, MAPKs and NF-κB pathways to show neuroprotective effects. RG dose-dependently alleviates muscle tension dysfunction, striatal lesions, and neuronal loss [36]. Additionally, gintonin and ginsenosides Rg3, and Rf prevented mHTT aggregation in both in cells and in animal model experimental models [96,97]. Gintonin

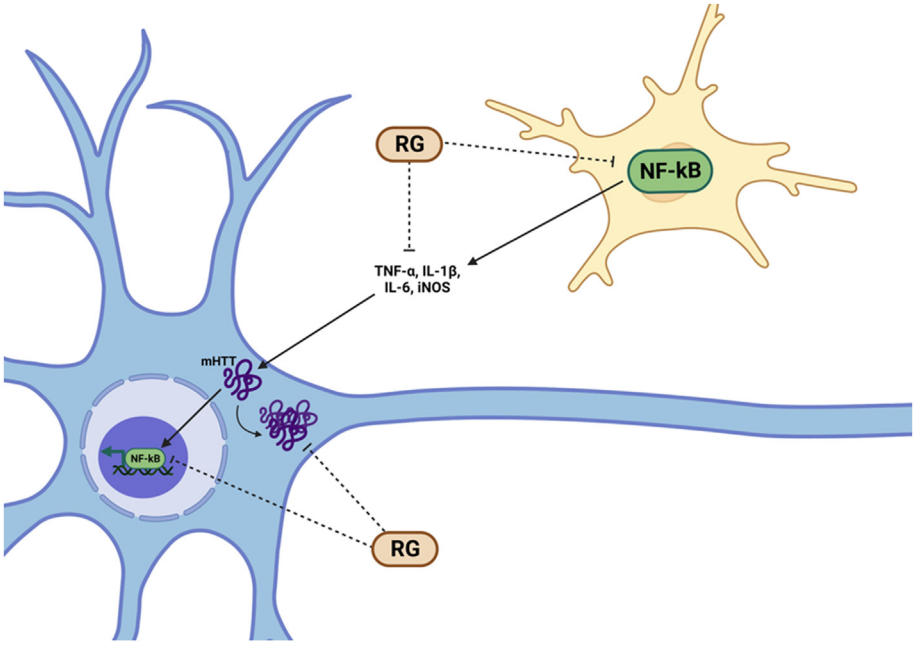

Fig. 7. Effects of Red ginseng on neuroinflammation in Huntington's disease
Red ginseng inhibits the formation and aggregation of mHTT and downregulates the activation of NF-κB in neurons and microglia. By suppressing the activation of microglia, red ginseng decreases inflammatory cytokines and factors, thereby alleviating neuroinflammation and Huntington's disease symptoms.

inhibits the mRNA expression of TNF-α, IL-1β, IL-6, iNOS, and COX-2 [96]. It also suppresses the activation of microglia via the reduction of the MAPK and NF-κB pathways. Additionally, Rg3 and Rf regulate the p53-Bax-related mitochondrial apoptotic pathway, indicating that Rg3 and Rf treated HD by alleviating mHTT aggregation, mitochondrial dysfunction, and apoptosis [97].

In summary, these results suggest that RG improves the neuroinflammatory response in HD by preventing the formation and aggregation of mHTT and by down-regulating inflammatory factors and pathways (Fig. 7).

2.4. Amyotrophic lateral sclerosis

ALS is a neurodegenerative disease featured by the progressive loss of motor neurons in the brain and spinal cord [98]. Mutant aggregation and the RNA binding protein FUS, TAR DNA-binding protein 43, and superoxide dismutase-1 (SOD1) are involved in neurodegeneration in ALS. The primary symptoms of ALS include frontotemporal dementia (FTD), dysphagia, dysarthria, respiratory insufficiency, and muscle atrophy.

Neuroinflammation in ALS exacerbates disease progression. Expression of mutant SOD1 (mSOD1) activates microglia [99]. The expression of mSOD1 increases the secretion of the inflammatory cytokine TNF-α.

Ginseng prolongs the onset of signs and survival in ALS [100], and RG components relieve neuroinflammation caused by ALS. For example, ginsenoside Re and gintonin alleviate the symptoms of ALS by exerting anti-neuroinflammatory effects in animal models of ALS [101,102]. Re mitigated the symptoms of ALS by inhibiting the loss of motor neurons, the secretion of TNF-α, and the activation of microglia and astrocytes [101]. Gintonin shows anti-inflammatory effects by reducing Iba-1 and by improving motor function [102].

Collectively, RG and its components may serve as medicinal plants that delay ALS symptoms and alleviate ALS by exerting anti-inflammatory effects. However, little research has been conducted on ALS and RG; therefore, further research is needed.

3. Conclusion

RG and its components have been shown to have beneficial effects in various fields such as inflammatory response, oxidative stress, and cancer. Many studies have consistently shown that RG can effectively treat neurodegenerative diseases such as AD, PD, HD, and ALS. Recently, neuroinflammation has emerged as a pathogenesis of neurodegenerative diseases, and RG helps alleviate neurodegenerative disorders by regulating the neuroinflammatory response. RG relieves neuroinflammation by down-regulating the NF-κB and MAPK pathways; reducing the expression of inflammatory factors TNF-α, IL-1β, IL-6, COX-2, and iNOS; and inhibiting the activation of microglia. In addition, Aβ, tau protein, α-syn, and mHTT, which act as etiologies in each neurodegenerative disease, also caused neuroinflammation. RG also improves neuroinflammation by reducing the accumulation or aggregation of pathogenic factors. Tables 1–3 summarizes the anti-inflammatory

Table 1
The Anti-neuroinflammatory Effects of Ginsenoside Panaxadiol

Panaxadiol	Symptoms	Effects	Reference
Rb1	AD	↓TNF-α, IL-1β, IL-6 ↓Microglia activation	[52]
		↓Tau hyperphosphorylation	[71]
		↓TNF-α, iNOS ↓Neuroinflammation	[73]
		↑IL-10 in hippocampus : Anti-inflammatory effect	[74]
	PD	↑Protected DA neurons in SNpc ↑DA neurotransmitters in the SNpc ↓DA neuronal damage ↓ NF-κB pathway in microglia of SNpc ↓Activated microglia/macrophage ↓TNF-α, IL-1β, iNOS, COX-2	[83]
		↓Pre-formed α-syn fibrils ↓α-syn fibrillation and toxicity	[92]
Rd	AD	Neuroprotective effect ↑ Cognitive abilities ↓Activation of the NF-κB pathway ↓TNF-α, IL-1β, IL-6, IL-8 ↑IL-10	[59]
		↓Tau hyperphosphorylation ↓Tau phosphorylation ↓Neuroinflammation Neuroprotective effect	[70]
	PD	Protected dopaminergic neuron ↓NO: anti-inflammatory effect	[85]
		Anti-inflammatory effect: ↓iNOS and COX-2 ↓NO, PGE2	[86]
Rg3	AD	↓Neuroinflammation: ↓ iNOS, TNF-α, IL-1β, IL-6 ↓Microglia activation	[51]
	HD	↓mHtt aggregation-positive cells ↓Mitochondrial dysfunction, apoptosis	[97]
Rh2	AD	↓ TNF-α, IL-1β, IL-6 in activation of microglial Anti-inflammatory effect ↓ Neuroinflammation	[53]
Rg5	AD	↓ Neuroinflammatory ↓ TNF-α and IL-1β ↓ cognitive deficit	[46]

Table 2
The Anti-neuroinflammatory Effects of Ginsenoside Panaxatriol

Panaxatriol	Symptoms	Effects	Reference
Re	PD	Protected dopaminergic neurons	[85]
	ALS	↓Loss of motor neurons, ↓Secretion of TNF-α ↓Activation of microglia, Astrocytes	[101]
Rg1	AD	↓Nerve damage ↓APP expression ↓Aβ deposition	[60]
		↓Tau phosphorylation ↓Oxidative stress, Apoptosis ↓Neuroinflammation	[29]
	PD	↓Nuclear transcription of NF-κB ↓Polarization of M1 microglia ↓IL-6, TNF-α, IL-1β ↓DA neuron loss, Behavior defects	[38]
		↑Glutamate receptor (GR) ↓NF-κB & MAPK pathways ↓TNF-α, IL-1β, NO ↑Survival of TH positive neurons.	[84]
		Protected TH-positive cell ↑CD3+CD4+ to CD3+CD8+ T cells in blood ↑CD4+ CD25+ Foxp3+ regulatory T cells in blood ↓ TNF-α, IFN-γ, IL-1β, IL-6 in serum	[87]
		↓ TNF-α, IL-1β in SNpc ↓ Formation of α-syn ↑ Motor coordination ↓ Loss of dopamine neurons	[30]
	HD	↓Behavioral defects ↓Body weight, Neuronal loss ↓Striatal morphological damage ↓Production of TNF-α, IL-1β ↓Striatal microglial activation ↓MAPKs & NF-κB pathways	[95]
Rh1	AD	↓MAPK & NF-κB in microglia ↓Neuroinflammation ↑IL-10 Anti-inflammatory effect	[28]
Rf	HD	↓mHtt aggregation-positive cells ↓Mitochondrial dysfunction, Apoptosis	[97]

Table 3
The Anti-neuroinflammatory Effects of RG Related Others

Compounds	Symptoms	Effects	Reference
Ginsenoside	AD	↓The expression of p-tau ↓Damage of hippocampus	[68]
RG	AD	↓Neuroinflammation, Microglia activation ↓iNOS, TNF-α, IL-1β, and IL-6	[50]
		↓Neuroinflammation ↓iNOS, TNF-α, IL-1β,IL-6 ↓Microglia & NF-κB pathway activation ↓Tau aggregation & phosphorylation ↑Tau degradation	[67]
	PD	↓IL-1β, IL-6, TNF-α, iNOS, COX-2 ↓Activation of microglia	[80]
		↓Neuroinflammation ↓NF-κB pathway & TNF-α ↓Oxidative stress, Apoptosis ↑Neuroprotective effects	[82]
	HD	↓Muscle tension dysfunction ↓Striatal lesions, Neuronal loss ↓Activation of microglia ↓iNOS, TNF-α, IL-1β, IL-6 ↓MAPK/NF-κB pathway in striatum ↓Neuroinflammation & Striatal toxicity	[36]
RG Oil	AD	↓Neuroinflammation ↓TNF-α, iNOS, COX-2 ↓MAPK, NF-κB pathway	[37]
		↓MAPK/NF-κB pathway & Inflammation ↓Neuronal apoptosis, oxidative stress	[47]
GTS	AD	↓iNOS, TNF-α, IL-1β, IL-6 ↓Microglia activation, Neuroinflammation	[50]

(*continued on next page*)

Table 3 (*continued*)

Compounds	Symptoms	Effects	Reference
NFP	AD	↓Iba-1 & Neuronal cell death ↑Neurogenesis in hippocampus	[55]
Gintonin	AD	↓TNF-α, p-NFκB ↓Amyloidogenic factors ↓ Cognitive & Synaptic dysfunction	[54]
	PD	↓IL-6, TNF-α, COX-2 ↓MAPK, NF-κB pathways ↓Microglia activation, Neuroinflammation ↑Protect DA neurons	[81]
		↓α-syn aggregation & TNF-α, COX-2	[91]
	HD	↓IL-1β, IL-6, TNF-α, COX-2, iNOS ↓Activation of microglia ↓MAPK, NF-κB pathway ↓mHTT aggregation	[96]
	ALS	↓Iba-1 ↑Motor function	[102]

effects of RG on mitigating neuroinflammation in neurodegenerative diseases. Taken together, RG and its components may help to alleviate neurodegenerative diseases such as AD, PD, and HD by regulating neuroinflammation. RG and its components have been demonstrated to exert a favorable impact on neuroinflammation in neurodegenerative diseases through a variety of *in vivo* and *in vitro* experiments. Nonetheless, to the best of our knowledge, no clinical evidence exists regarding RG's effect on the inflammatory response in patients with degenerative diseases. A bibliometric analysis of global clinical trials revealed that RG alleviated inflammation in patients with chronic organ inflammation or immune disorders [103]. Consequently, additional research is necessary to examine the potential of RG and its components in mitigating neuroinflammation in individuals with neurodegenerative diseases. To determine the clinical efficacy of red ginseng, several factors must be considered, including appropriate patient dosages, potential side effects, and usage guidelines.

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