Ginsenosides as selective glucocorticoid drugs: agonists, antagonists, and prodrugs

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Chapter 2

Ginsenosides as promising anti-inflammatory drugs: past and future

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Submitted

Abstract

Ginsenosides are a class of compounds from Chinese medicinal herbs such as *Panax ginseng* C.A. Mayer. They are used in treating various diseases, including various inflammatory disorders because they interfere with many signaling pathways. In most cases, their mechanism of action is unclear. Understanding the molecular mechanisms of ginsenosides' actions is challenging due to the wide variation in structure and the large number of possible targets. Here, we have performed a literature study on the anti-inflammatory effects of ginsenosides to provide an overview of what is known about their possible therapeutic effects and their mechanism of action. Ginsenosides present their anti-inflammatory effects in disease models for inflammatory disease and several neurological disorders. These effects are most likely due to these compounds' activation of the glucocorticoid receptor. Interestingly, ginsenosides function as selective glucocorticoid receptor agonists, inducing only partial activation of this receptor. As a result, ginsenosides exert their anti-inflammatory effects in different animal models without triggering side effects. In conclusion**,** unraveling the molecular mechanism underlying the selective activation of the glucocorticoid receptor by ginsenosides may provide valuable insights for further development of selective glucocorticoid receptor agonist drugs with effective anti-inflammatory action and reduced side effects.

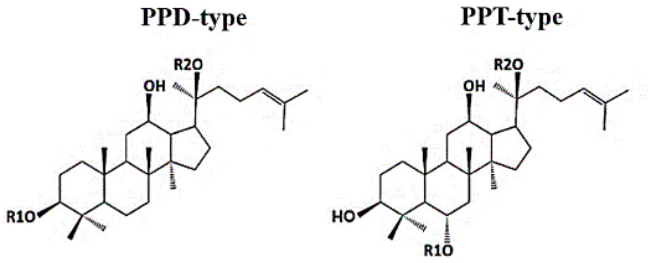
1. Introduction

Ginseng Radix (*Panax ginseng* C.A. Mayer) is one of the world's most widely used herbal medicines. It has a lengthy history of medical applications, and it has been used for its immunomodulatory, vaso-relaxation, anti-oxidant, and anti-aging effects in the treatment of wound healing and various diseases, including many types of cancer and inflammatory diseases (Leung and Wong 2010; Wong 2010; Kang and Min 2012; Kim 2018; He et al. 2018). Ginseng contains a wide variety of chemicals, such as polysaccharides, peptides, polyacetylene alcohols, fatty acids, phenolic compounds, and ginsenosides. Among these diverse constituents, ginsenosides are recognized as ginseng's principal and the most active class of compounds (Leung and Wong 2010; Wong 2010; Kang and Min 2012; Kim 2018; He et al. 2018). Ginsenosides are known as saponins (or sapogenin glycosides), which consist of a steroid or triterpene sapogenin backbone structure consisting of 17 carbons in a 4-ring structure, to which one or more acyl and/or glucose groups are attached (Leung and Wong 2010; Kang and Min 2012; Kim 2018; He et al. 2018) (Fig.1).

Depending on the structure of the aglycone backbone, ginsenosides can be categorized into three different types: a) the dammarane type, including protopanaxadiols (PPDs) and protopanaxatriols (PPTs), which are distinguished based on the existence of a hydroxyl group at carbon position 6 (C-6) on the backbone structure. PPDs include ginsenosides PPD, Rb1, Rb2, Rc, Rd, Rg3, Rh2, F2, and compound K, and PPTs include ginsenosides PPT, Rg1, Re, Rf, Rg2, F1 and Rh1; b) the oleanane (oleanolic acid) type, such as Ro and polyacetylene-ginsenoside Ro; c) The ocotillol types, such as the majonosides R1, R2, vina-R1, vina-R2, vina-R6, vina-R14, 24-pseudoginsenoside RT4 and pseudoginsenoside F11 (Leung and Wong 2010; Kang and Min 2012; Kim 2018; He et al. 2018). Differences in the nature of acyl substituents and glucose groups at C-3, -6, and -20 are additional distinguishing factors. The steroid-like structures make ginsenosides hydrophobic, which enables them to diffuse through the lipid bilayer of the cytoplasmic membrane (Leung and Wong 2010; Kang and

Min 2012; Kim 2018; He et al. 2018). The addition of glucose moieties makes ginsenosides more hydrophilic, which prevents free diffusion through the membrane and their cell entry requires the action of glucose transporters (Shang et al. 2008; Wang et al. 2018).

Here, we describe the results of a literature review of the pharmacological roles of PPT and PPD- types of ginsenosides. We focused on their potent anti-inflammatory effects and the elucidation of the mechanism of action, which is essential to enable the exploitation of the ginsenosides' potential as anti-inflammatory drugs. Based on the information from the literature studies, we showed that ginsenosides present potent anti-inflammatory effects without triggering side effects. Ginsenosides mediate their anti-inflammatory effects, selectively dependent on GR. Unraveling the molecular mechanism of ginsenosides as selective GR modulators may open up a new approach toward synthesizing novel anti-inflammatory GC drugs with reduced side effects.



PPD-type	R1	R2	PPT-type	R1	R2
Rb1	Glc-Glc	Glc-Glc	Re	Glc-Rha	Glc
Rb2	Glc-Glc	Glc-Arap	Rf	Glc-Glc	H
Rc	Glc-Glc	Glc-Araf	Rg1	Glc	Glc
Rd	Glc-Glc	Glc	Rg2	Glc-Rha	H
F2	Glc	Glc	F1	H	Glc
Rg3	Glc-Glc	H	Rh1	Glc	H
Rh2	Glc	H	PPT	H	H
Compound K	H	Glc			
PPD	H	H			

Figure 1. *Structures of PPT-type and PPD-type ginsenosides. Functional groups are indicated as follows. Glc: β-D-glucopyransosyl; Arap: α-L-arabinopyranosyl, Rha:α-L-rhamnopranosyl.*

2. Methodology

The databases PubMed/MEDLINE with the keywords "ginsenosides" along with ''pharmacology effects'' were used. There were 3550 papers. When we used "ginsenosides" along with ''anti-inflammatory'' effects as combination keywords, Seven hundred fifty papers have been published since the 2000s. To make our search more specific, we used "ginsenosides" along with ''anti-inflammatory'' effects, along with the "mechanistic effects'', "metabolic system," "endocrine system," or "nervous system," There have been 25, 109, 120, and 120, papers, respectively. Then, relevant manuscripts published before November 2022 were collected, curated, and critically evaluated to extract necessary information. The chemical structures of ginsenosides were illustrated following PubChem with the help of E- Notebook 19 via Citrix.

3. Metabolism of ginsenosides

Glycosylated ginsenosides (e.g., Rg1, Rb1) can be transformed into partially de-glycosylated (e.g., F1, F2) and aglycone forms (e.g., PPT, PPD) via chemical or enzymatic cleavage of functional glucose groups attached by glycosidic bonds (Chin et al. 2006; Leung and Wong 2010; Kang and Min 2012; Yu et al. 2017; He et al. 2018). The key enzymes mediating the transformation of ginsenosides in our body are β-glucosidases from the microbiome in the gastrointestinal tract (GIT) and endogenous β-glucosidases (Bae et al. 2002; Bae et al. 2004; Chin et al. 2006; Leung and Wong 2010; Zheng et al. 2017). Due to these enzymatic activities, ginsenosides are gradually converted from their glycosylated to aglyconic forms in a series of step-wise-deglycosylation reactions (Bae et al. 2004; Chin et al. 2006; Leung and Wong 2010). Accordingly, it has been reported that Rg1 transforms into ginsenosides Rh1, F1, and PPT via a series of deglycosylation reactions in a rat model (Feng et al. 2010). Another study reported that ginsenoside Re (PPT-type) which has two glucose groups at C-6, is transformed to Rh1 or F1 in the GIT (Bae et al. 2005).

After oral administration of Rg1 in rat models, metabolites of Rg1 were detected in feces and urine. Due to deglycosylation and oxygenation, Rg1 was transformed to mono-oxygenated Rg1, Rh1, and the secondary metabolite mono-oxygenated PPT (Wang et al. 2014). Additionally, ginsenoside Rg3 was metabolized by β-glucosidases of human intestinal bacteria to ginsenosides Rh2 and PPD when Rg3 was incubated with isolated intestinal bacterial strains (Bae et al. 2002; Bae et al. 2004). Moreover, it was reported that ginsenoside Rg3 is converted to Rh2 after one hour and to PPD after four hours when administered orally or intravenously (Peng et al. 2016). The conversion rate was higher after oral compared to intravenous administration (9.7 % versus 7.9 %)(Peng et al. 2016). The higher conversion rate after oral administration indicated that enzyme activity in the intestine is involved in the metabolism of glycosylated ginsenosides. However, this study also showed that the transformation could happen in both the systemic circulation and during the absorption process in the GIT (Peng et al. 2016).

Additional studies confirmed that the metabolism of ginsenosides might yield different metabolic products, depending on the administration route. When Rd was administered orally, partially de-glycosylated Rg3 was the primary metabolite detected. However, Rb1 was the dominant metabolite when administered intravenously due to the different metabolic pathways (Yang et al. 2007). Additionally, microbial transformation of

ginsenosides Rb1, Re, and Rg1 produced 12 metabolites, including 6 new intermediate metabolites. Those intermediate metabolites were transformed over 96 h by deglycosylation and dehydrogenation to four rare ginsenosides (Rd, GypXVII, Rg2 and PPT) with 38–96% yields. Those four ginsenosides exert more potent anti-inflammatory activities compared to their precursors. They significantly attenuated the production of TNF-α in lipopolysaccharide (LPS)-induced murine RAW264.7 macrophages and the xylene-induced acute inflammatory model of mouse ear edema (Yu et al. 2017).

Rapid metabolism of ginsenosides was observed after oral administration of ginsenosides Rg1 and Rb1 to rats (Han et al. 2006; Han and Fang 2006). Meager amounts of ginsenosides Rg1 and Rb1 were detected in serum (Han et al. 2006; Han and Fang 2006). In line with these results, it has been reported that Rb1 was absorbed more slowly than Rg1 after oral administration (Xu et al. 2003). The oral bioavailability of Rb1 was 4.35% after 1.5 h, while the oral bioavailability of Rg1 was 18.40% after 1 h. These data indicated that the PPT group of ginsenosides exhibit better oral bioavailability than the PPD group (Xu et al. 2003). These results may be associated with the slower metabolic changes of PPT-type than PPD-type ginsenosides (Qi et al. 2011). To increase the bioavailability of ginsenosides, several strategies are being investigated, including co-administration of ginsenosides with adrenaline, emulsification of ginsenosides into a lipid-based formulation (Leung and Wong 2010), and chemically or enzymatically converting glycosylated ginsenosides to partially glycosylated or aglycone ginsenosides via the microbiome or endogenous β-glucosidases (Bae et al. 2002; Bae et al. 2004; Chin et al. 2006; Han et al. 2006; Han and Fang 2006; Leung and Wong 2010; Zheng et al. 2017).

Additionally, ginsenosides are metabolized in the gastrointestinal tract (GIT) and the liver by oxygenation reactions catalyzed by hepatic cytochrome P450 (Hao et al. 2010). An oxidation reaction (besides deglycosylation) occurs in the GIT, where PPD-type ginsenosides Rb1, Rb2, Rc, and Rd are converted to CK, while ginsenosides Rg3 and Rg5 are converted to Rh2 and Rh3, respectively (Qi et al. 2011; Won et al. 2019). In conclusion, research into ginsenosides should take into account that these compounds are rapidly metabolized and that multiple metabolic products may be responsible for the observed biological activities.

4. Pharmacological effects of ginsenosides in inflammatory diseases

Inflammation is a pivotal biological response of the body required for its defense against pathogens, restoring cellular homeostasis, and repairing damaged tissue after injury. Different signaling pathways mediate the inflammatory response, including the activation of Toll-like receptors (TLRs), the function of transcription factors such as Nuclear Factor-kappa B (NF-κB) and Activator Protein-1 (AP-1), and the expression of pro-inflammatory cytokines (TNF-α, interleukin (IL)-1b, IL-6, and INF-g) and chemokines (IL-8, CCL2 and, CXCL11) (Kawai and Akira 2007; Alderton and Scanlon 2021). As a result, immune cells such as neutrophils, macrophages, and lymphocytes infiltrate into the affected tissue to eliminate pathological invaders. Neutrophils are the primary responders recruited to the injured tissue and mediate the pro-inflammatory response (Amulic et al. 2012; de Oliveira et al. 2016). The recruitment of neutrophils further triggers the activation and migration of macrophages, which clean up apoptotic neutrophils and stimulate the antimicrobial activity of neighboring immune cells (Watanabe et al. 2019). Once inflammation is resolved, macrophages shift from a pro-inflammatory (M1) to an anti-inflammatory/pro-resolution

(M2) phenotype and restore cellular and tissue homeostasis (Watanabe et al. 2019). However, in chronic inflammatory disorders, there is a failure to resolve inflammation, which can trigger tissue damage and loss of function. Long-term inflammation is associated with several disorders and neurological diseases (McGeer and McGeer 2004; Alam et al. 2016; Singh et al. 2016). In this review, we discuss the anti-inflammatory effects of ginsenosides in different diseases characterized by inflammation and immune system disorders (Fig.2). Altogether, the presented data indicate that ginsenosides of the PPD- and PPT-types are effective for treating these diseases and may provide novel avenues for the development of anti-inflammatory drugs.

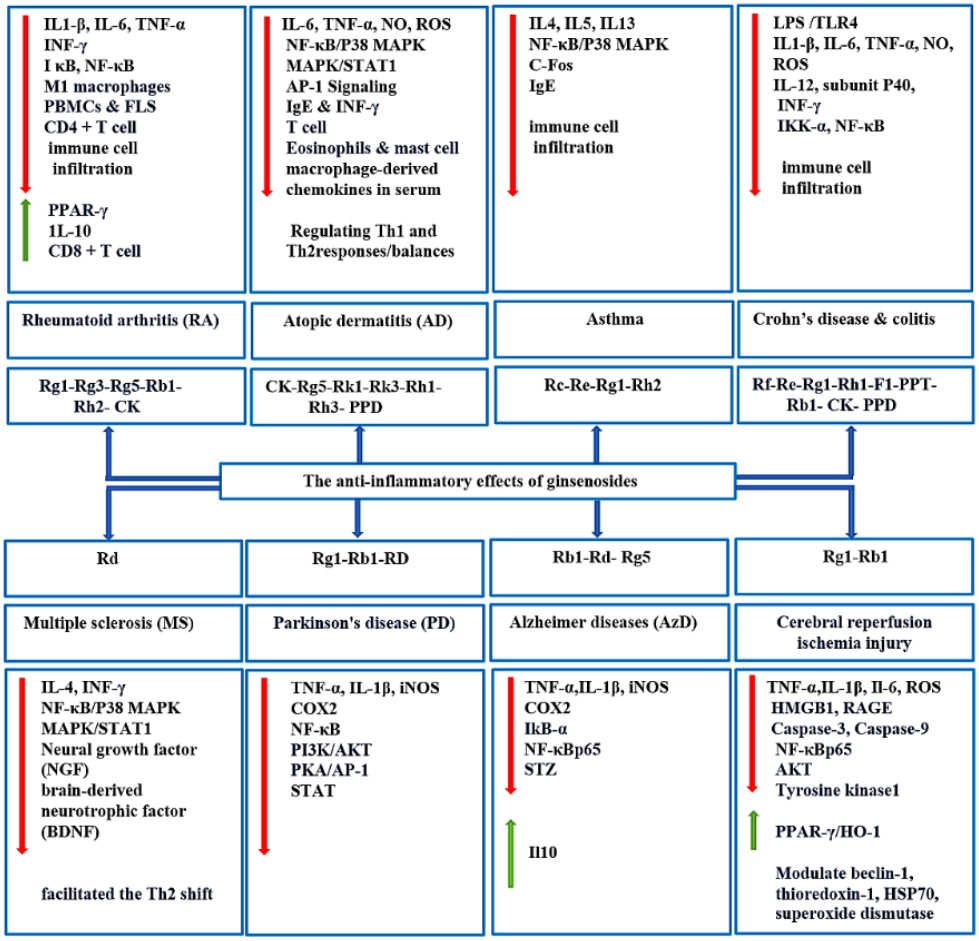


Figure 2. *The anti-inflammatory effects of ginsenosides in several immune-related disorders and neurological diseases. The green color indicates an up-regulation. The red color indicates a downregulation.*

4.1. Therapeutic effects of ginsenosides in inflammatory diseases

Rheumatoid arthritis (RA) is an autoimmune disease characterized by cartilage and bony destruction that causes disability and threatens the health of humans (Smolen et al. 2018). It has been reported that ginsenosides Rg1, Rg3, Rg5, Rb1, Rh2, and CK showed a significant therapeutic effect on acute arthritis (Zhang et al. 2021). However, ginsenoside CK showed the most effective effects in the collagen-induced arthritis (CAIA) model in mice (Tang et al. 2021; Zhang et al. 2021).

CK decreased the swelling, redness, functional disorders of joints, and pathological changes in CAIA mice. In addition, CK increased CD8+ T cell to suppress the immune response, reduced the number of activated CD4+ T cells and pro-inflammatory M1 macrophages, and suppressed the secretion of pro-inflammatory cytokines such as TNF-α and IL-6 (Zhang et al. 2021). Moreover, CK inhibited the expression of TNF-α in the joints of CAIA mice (Liu et al. 2014). Finally, CK inhibited pro-inflammatory cytokines TNF-α, IL−1β, IL-6, interferon-γ (IFN-γ), and IL-17 levels, and increased the expression of anti-inflammatory cytokine IL-10 levels in serum in CAIA mice and in adjuvant-induced arthritis (AIA) rats (Wu et al. 2014).

Another study reported that Rb1 suppressed TNF-α upregulation in Peripheral Blood Mononuclear Cells (PBMCs), fibroblast-like synoviocytes (FLS), and chondrocytes induced by IFN-γ, LPS, or IL-1. Therefore, Rb1 ameliorated the clinical arthritis score in the CAIA mice. Histological studies demonstrated that Rb1 reduced inflammatory cells infiltration and cartilage destruction in the arthritic joint (Kim et al. 2007).

Another ginsenoside, Rg1, significantly attenuated joint swelling and injuries in the AIA rat model. Rg1 decreased the level of TNF-α and IL-6, elevated peroxisome proliferator-activated receptor γ (PPARγ) protein expression, suppressed IκBα phosphorylation and NF-κB nuclear translocation in the inflammatory joints of AIA rats and in RAW264.7 cells stimulated by LPS (Zhang et al. 2017). Importantly, it has been presented that Rg1 was shown to have anti-inflammatory effects in CAIA mice, without adverse effects on glucose levels or osteoblast proliferation and differentiation (Du et al. 2011). These data indicated that ginsenosides are potential candidates for the treatment of RA, with strong anti-inflammation and immune-modulating capabilities.

Atopic dermatitis (AD) is a skin disease caused by dysregulation of the inflammatory response. Itchiness, the most apparent symptom of AD, can lead to skin inflammation due to scratching or rubbing (Cipriani et al. 2014). Patients show elevated levels of Th17-associated cytokines in skin cells (e.g., IL-17A, IL-6, IL-23, IL-4, and IL13) (Brandt and Sivaprasad 2011). Immunoglobulin E (IgE) production and eosinophil recruitment are elevated, leading to an increase in the risk for *AD* development (Brandt and Sivaprasad 2011). Interestingly, ginsenoside PPD has shown potent effects for treatment of in a mouse model for AD (Kim et al. 2013). Oral administration of PPD in mice reduced the dermatitis score, scratching time, ear thickness, and acuteness of skin lesions. In addition, PPD treatment decreased the levels of macrophage-derived chemokines in serum, the infiltration of eosinophils and mast cells in the skin, and the production of pro-inflammatory/T cell-related cytokines in splenocytes (Kim et al. 2013). Additionally, ginsenoside Rg5 and its metabolite ginsenoside Rh3 inhibited oxazolone-induced dermatitis in mice and accordingly decreased the serum levels of IgE and IL-6 (Shin et al. 2006). In

addition, the infiltration of inflammatory cells and granulation of mast cells decreased significantly.

In cell culture models for AD, cells of a keratinocyte cell line (HaCaT) were treated with TNF-α/IFN-γ and cells from the RAW264.7 macrophage cell line were activated with LPS (Ahn et al. 2016; Lee and Son 2011; Shin et al. 2006). Introducing Rh3 or Rg5, alone or in combination with Rk1, in both cell lines decreased the production of nitric oxide (NO), reactive oxygen species (ROS), pro-inflammatory cytokines and thymus-activation and regulation chemokine (TARC). Furthermore, these ginsenosides inhibited the NF-κB/p38/MAPK (classical mitogen-activated protein kinase) signaling (Ahn et al. 2016; Shin et al. 2006). It was reported that administration of Rg3 and/or Rh1 to keratinocytes activated by high-affinity IgE receptor (FcεRIa)-stimulated basophils suppressed the p70S6K signaling pathway, which is known to be involved in AD-related inflammation (Zheng et al. 2011). These data indicate that ginsenosides Rg5, Rk3, Rg3, and Rh1 are promising candidates for treating patients with AD (Osada-Oka et al. 2018).

Asthma is a heterogeneous disorder identified by chronic inflammation of the respiratory airways that can be stimulated by allergen exposure (McCracken et al. 2017). Ginsenoside Rh2 induces potent attenuation of the allergic response in the airways in a mouse model for *asthma*. Ginsenoside Rh2 inhibits inflammatory cells, decreases serum levels of IL-4, IL-5, and IL-13, the IgE and also NF-κB activity in lung tissue (Li et al. 2015). Accordingly, ginsenoside Rh2 inhibits the activity of NF-κB and the phosphorylation of p38 and MAPK in the same asthmatic mouse model (Lee et al. 2018a). Rh2 as well as Rc, Re, and Rg1 also showed significant immune-suppressive effects by decreasing the total immune cell numbers in the bronchoalveolar lavage fluid of mice (Lee et al. 2018a). In addition, ginsenoside Re, administrated orally, suppressed the action of MAPK, NF-κB, and c-Fos in a lung epithelial cell line (A549) and in alveolar macrophages (MH-S)(Lee et al. 2018a). Collectively, these data indicate that ginsenosides Rh2, Rc, Re, and Rg1 could alleviate asthmatic symptoms.

Crohn's disease and ulcerative colitis are heterogeneous chronic autoimmune bowel diseases with genetic, immunological, and environmental components related to the GIT, characterized by increased expression of TNF-α, IL-12 subunit p40, IL-1β, IL-6, and IFN-γ, and high levels of NO and ROS (McGuckin et al. 2009; Rosen et al. 2015). Current intervention strategies for treating both diseases are surgery or immunosuppressant medical therapies with the glucocorticoid drug prednisone, TNF inhibitors, and azathioprine (Okobi et al. 2021). In dextran sodium sulfate–promoted colitis in mice, ginsenosides CK, Rh1, F1, and PPD relieved the severe symptoms of colitis and inhibited the facilitation of macrophages in colonic tissue. Those Ginsenosides suppressed the expression of the pro-inflammatory cytokines TNF-α, IL-12 subunit p40, IL-1β, IL-6, and IFN-γ in LPS-stimulated RAW264.7 macrophages and in peritoneal macrophages (Seong et al. 2015). The mechanism causing the potent effects of ginsenosides was based on the inhibition of the NF-κB signaling pathway (Seong et al. 2015). In addition, ginsenoside Rf has been found to reduce the production of inflammatory agents such as IL-1β, IL-6, TNF-α, NO, and ROS in intestinal epithelial cells (HT-29) and mouse macrophages (RAW264.7) stimulated by TNF-α (Ahn et al. 2016). Ginsenoside Rb1 inhibits LPS-regulated phosphorylation and degradation of IRAK-1. As a result, Rb1 prevents IKK-α phosphorylation, NF-kB activity, and

the production of pro-inflammatory cytokines, such as TNF-α and IL-1β, in a mouse model of colitis (Joh et al. 2011). Ginsenoside Re shows anti-inflammatory effects by suppressing the interactions between LPS and TLR4 in macrophages (Lee et al. 2012). Re also effectively suppresses gene expression of IL-1β and TNF-α, decreases NF-κB activity and inhibits myeloperoxidase activation and colon shortening *in vivo* in a 2,4,6-trinitrobenzene sulfonic acid (TNBS)-stimulated colitis mouse model (Lee et al. 2012). Ginsenoside Rg1 and it metabolites PPT, Rh1, and F1 remarkably improve the symptoms in this model by targeting the activation of the NF-κB signaling pathway (Lee et al. 2015). Therefore, ginsenosides Rf, Re, Rg1, Rh1, F1, PPT, Rb1, CK, and PPD present a potential treatment option to relieve *Crohn's* disease and ulcerative colitis.

4.2. Anti-inflammatory effects of ginsenosides in neurological diseases

Multiple sclerosis (MS) is a chronic autoimmune disease in the central nervous system, hallmarked by inflammatory demyelination (Dobson and Giovannoni 2019). In MS, myelin is targeted by host immune cells, which causes loss of motor functions, mood disturbance, cognitive dysfunction, and other neurological damage (Dobson and Giovannoni 2019). Intraperitoneal administration of ginsenoside Rd to myelin oligodendrocyte glycoprotein (MOG)-stimulated *MS* mice greatly relieved the clinical intensification of the disease, decreased the permeability of the blood-brain barrier, reduced IFN-γ levels, regulated the expression of IL-4 and facilitated the Th2 shift in splenocytes and cerebral cortex (Lee et al. 2018b). Rd elevated the levels of neural growth factor and brain-derived neurotrophic factor (BDNF) in both the cerebral cortex and lumbar spinal cord of *MS* mice, suggesting that Rd stimulates the release of these neurotrophic factors for maintenance and recuperation from pathological loss (Lee et al. 2018b). Intrathecal pretreatment of rats with ginsenoside Rg1 and Rb1 also relieved behavioral impairment in the MOG-stimulated chronic *MS* mouse model (Lee et al. 2018b). These data indicate that ginsenosides Rd, is a promising novel starting point for the development of drugs that alleviate MS.

Parkinson's disease (PD) is a neurodegenerative disease associated with the loss of dopaminergic neurons (Schneider et al. 2017). Ginsenosides Rg1 and Rb1 and their metabolites have been shown to alleviate *PD* symptoms in mouse and rat models (Zheng et al. 2018). Rb1 and Rg1 regulate microglial activation in mice, which is believed to underly their therapeutic effects in neurodegenerative diseases, including PD (Lee et al. 2013; Zhou et al. 2016). Rg1 treatment improved the behavioral deficits of *PD* mice in the pole test (behavior test to assess movement disorders in mice) and decreased the loss of dopaminergic cells that were stimulated via 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (Jiang et al. 2015; Van Kampen et al. 2014; Zhou et al. 2016).

In i*n vitro* studies, Rg1 also inhibited the expression of iNOS, COX-2, TNF-α, IL-1β, and NF-κB after LPS-stimulation of microglial cells (Hu et al. 2011; Gao et al. 2019). Furthermore, ginsenosides such as Rg1, Rb1, and Rd have also been found to exert antiapoptotic, antioxidant, and anti-inflammatory effects in cell-based PD models (Radad et al. 2011). Several signaling pathways have been implicated in these effects of ginsenosides, including the NF-κB, PI3K/AKT, PKA/AP-1 and JNK/AP-1, and STAT signalling (Radad et al. 2011; Hu et al. 2011; Lee et al. 2012; Gao et al. 2019). Thus, both *in vitro* and *in vivo* studies support that ginsenosides Rd, Rg1, and Rb1 alleviate symptoms of PD, most likely through their regulatory action son microglia cells.

Alzheimer's disease (*AzD*) is a neurodegenerative disease associated with progressive loss of memory and cognitive functions (Hardy and Selkoe 2002). AzD is mainly related to the aggregation of amyloid β-proteins (Aβ) (Hardy and Selkoe 2002). In the AzD rat model established by injecting Aβ peptides into the hippocampus bilaterally, data presented that ginsenoside Rd, reduced the expression of genes encoding pro-inflammatory proteins such as IL-1β, IL-6, and TNF-α, and increased the expression level of gene encoding the anti-inflammatory protein IL-10 (Liu et al. 2012). In another study performed in the Aβ-protein precursor transgenic mouse model, Rd suppressed the expression of the NF-kB subunit p65 (Liu et al. 2015). Therefore, Rd could improve learning and memory ability and reduce neuronal death and loss in the hippocampus in AzD mice. Another study illustrated that ginsenoside Rb1 suppressed the biomarkers of neuroinflammation cyclooxygenase-2 (COX-2), IkB-α, and iNOS (Wang et al. 2011). Additionally, in a streptozotocin(STZ)-induced memory-impaired rat model, ginsenoside Rg5 exerted inhibitory effects on neuroinflammation by suppressing COX2 and iNOS expression (Chu et al. 2014). These results indicate that ginsenosides Rd, Rb1, and Rg5 are potent candidates for treating *AzD*.

Cerebral reperfusion ischemia injury is a nervous system disorder that causes motor impairment, threatening human health and life (Livesay 2014). Nowadays, bone marrow mesenchymal stem cell (BMSC) transplantation has been used in treating cerebral ischemia disease. However, this method has some limitations due to a low neural cell conversion rate and slight proliferation ability (Livesay 2014). Cerebral ischemia-reperfusion injury can trigger inflammation and neuronal apoptosis in the ischemic and peripheral nerve cells (Livesay 2014). PPARγ and its downstream effector Heme oxygenase-1 (HO-1) suppressed inflammation and neuronal apoptosis in many different pathological conditions (Park et al. 2011; Aleshin et al. 2013) It has been reported that ginsenoside Rg1 acts like rosiglitazone as PPARγ agonist by activating PPARγ/HO-1 signaling. Rg1 reduced the levels of IL-1β, TNF-α, and high-mobility group box-1 (HMGB1), cleaved caspase-3, cleaved caspase-9, and receptor for the advanced glycation end product (RAGE) in rats (Yang et al. 2015). Another study showed that Rg1 decreased brain infarct volume and the permeability of the blood-brain barrier in an ischemic brain (Xie et al. 2015). Moreover, Rg1 suppressed the loss of mitochondrial membrane potential and inhibited ROS production in astrocytes (Sun et al. 2014).

Another ginsenoside, Rb1, suppressed the local inflammation in the ischemic hemisphere. Rb1 inhibited the NF-kB signaling pathway leading to the reduction of TNF-α and IL-6 levels (Xie et al. 2021). Additionally, Rb1 in mice reversed the induction of the Beclin-1 level, which is an indicator of autophagy activity in rats (Lu et al. 2011). Moreover, ginsenosides Rb1 and Rg1 could reverse the reduction of thioredoxin-1 and superoxide dismutase levels and modulated the expression of heat shock protein 70 (HSP70), Akt, and the NF-kB subunit p65 in mice subjected to middle cerebral artery occlusion (MCAO)(Zeng et al. 2014). Moreover, ginsenosides Rb1, Rg1, and notoginsenoside R1 in combination with Astragaloside IV (one of the major compounds from the aqueous extract of Astragalus membranaceus) presented protective effects on cerebral ischemia injury via anti-apoptosis and anti-inflammation activities. This combination inhibited the activation of the NF-kB, tyrosine kinase 1/signal transducer, and AP-1 signaling pathways and modulated endoplasmic reticulum stress after cerebral ischemia in mice (Huang et al. 2014). Collectively, ginsenosides Rg1 and Rb1 relieve the symptoms of neurological disorders, most likely as a result of their anti-inflammatory

effects. Thus, these ginsenoside effects may indicate a potential novel direction for drug development for treatment of neuroinflammatory diseases.

5. The molecular mechanisms underlying the anti-inflammatory effect of ginsenosides

Recent research has provided insight into the molecular mechanisms of action of ginsenosides underlying their effects as anti-inflammatory agents in different tissues. Here we summarize the current knowledge in this field.

5.1. Ginsenosides are selective glucocorticoids receptor agonists

It has been demonstrated that ginsenosides regulate the function of various receptors, e.g., receptor tyrosine kinases (RTK), serotonin (5-HT) receptors, N-methyl-D-aspartate (NMDA) receptors, and nicotinic acetylcholine receptors (AChR) (Leung and Wong 2010). However, the direct interaction of ginsenosides with the ligand binding sites of receptors has only been demonstrated for several steroid receptors, including the glucocorticoid receptor (GR), estrogen receptor, androgen receptor, and progesterone receptor (Lee et al. 2003; Leung et al. 2009; Li et al. 2009; Leung and Wong 2010). Specifically, ginsenosides Rg1 and its metabolites Rh1, Re, and PPT have been shown to be functional ligands of the GR (Leung et al. 2009; Leung and Wong 2010; Du et al. 2011; Karra et al. 2019; He et al. 2020).

Just like the other steroid receptors, the GR is a member of the nuclear receptor family and acts as a transcription factor upon activation by a ligand, regulating gene transcription through various mechanisms (Reichardt et al. 2000; Miranda et al. 2013; Vandevyver et al. 2014). It can transactivate genes by binding to specific target sites in the DNA which are called glucocorticoid response elements (GREs)(Ramamoorthy and Cidlowski 2016). Alternatively, it can interact with other transcription factors and thereby modulate their action. For example, GR is able to transrepress genes by physical interaction with transcription factors such as NF-kB and AP-1(Strickland et al. 2022). This latter mechanism by which GR represses gene transcription is generally considered to play a key role in the anti-inflammatory effects of glucocorticoids (GCs) because many genes encoding pro-inflammatory factors are activated by transcription factors such as NF-kB and AP-1 (Vandevyver et al. 2014; Strickland et al. 2022).

Synthetic ligands of the glucocorticoid receptor, such as beclomethasone, dexamethasone, and prednisone, are frequently utilized in strategies for treating inflammatory diseases (Alan 2017). They are widely used and are generally very effective in suppressing hyper-inflammation involved in many pathologies. However, GCs have a wide range of side effects that promote endocrine and metabolic disorders and cause reduced growth velocity, osteoporosis, diabetes, hypertension, weight gain, muscle weakness, wound healing disorders, and tissue degeneration (Alan 2017). Therefore, there has been a lot of interest in developing selective GR agonists that inhibit inflammation, but do not induce adverse effects on other body functions (Procopiou et al. 2001; Ryabtsova et al. 2016; Saksida et al. 2014). It has been reported that metabolites of PPD and PPT-type ginsenosides are functional ligands for GR (Leung et al. 2009; Leung and Wong 2010; Du et al. 2011; He et al. 2020; Karra et al. 2019; He et al. 2020). It has been published that PPD and PPT can bind to GR and trigger its nuclear translocation (Karra et al. 2018; Leung et al. 2009). Rg1 has been shown to bind to the human GR with an affinity 10–100 fold lower than dexamethasone,

thereby inducing transcriptional and non-transcriptional actions of the GR receptor in cultured cells (Leung et al. 2006a; Leung et al. 2006b). Thus, ginsenosides represent low-affinity agonists of GR, and their effects are not as potent as those of clinically used GCs (Du et al. 2011; He et al. 2020; Karra et al. 2019; Leung et al. 2009; Leung and Wong 2010).

It has been reported that most of the side effects of GCs are predominantly mediated via the transactivation activity of the GR, while most of the anti-inflammatory effects are triggered by GR's transrepression activity (Schäcke et al. 2004; Louw 2019). Therefore, it was hypothesized that the dissociation of transactivation from transrepression by a selective GR agonist might lead to the separation of the therapeutic effects from the side effects (Reichardt et al. 2000 ; Schäcke et al. 2004; Louw 2019). Recently, it has been demonstrated that ginsenosides, in particular Rg1, can specifically trigger the transrepression activity of GR without stimulating transactivation activity (Du et al. 2011; Karra et al. 2019). Therefore, ginsenosides induce anti-inflammatory effects with strongly reduced side effects. Rg1 suppressed LPS-induced pro-inflammatory cytokine secretion and inhibited nuclear translocation and DNA binding activity NF-κB in RAW264.7 and A549 cells. The negative effects of Rg1 on NF-κB activation are due to a reduction in IκB phosphorylation and protein stabilization, and these effects were mediated by GR. Importantly, Rg1 did not inhibit the proliferation or differentiation of mouse osteoblasts due to its inhibitory effects on LPS-induced MAPK activation. More importantly, Rg1 inhibited acute inflammation in the zymosan-induced inflamed paw model in mice and chronic inflammation in the CAIA mouse model, without triggering hyperglycemia or osteoporosis, unlike dexamethasone which did induce these side effects (Du et al. 2011). In agreement with this study, it was reported that ginsenosides PPT and PPD induce the transrepression activity of GR in human cells without triggering transactivation, and induce GR-dependent anti-inflammatory effects without triggering the typical side effects of classical GCs (Alan 2017; Du et al. 2011; Karra et al. 2018) (Fig.3).

Following up on these studies, we recently studied the anti-inflammatory effects of ginsenosides in detail in zebrafish. Our data showed that Rg1 has anti-inflammatory effects, which was reflected in an inhibition of the wound-induced neutrophil migration in the zebrafish tail-fin amputation model (He et al. 2020). The anti-inflammatory actions of Rg1 were abolished in a *gr-/-* mutant line, which indicated that the action of Rg1 was mediated by the zebrafish homolog of GR (Gr). Notably, we demonstrated that Rg1 induced transrepression activity of Gr on immune-related genes while not transactivating the classical Gr target genes *pck1* and *fkbp5* (He et al. 2020). Furthermore, Rg1 showed only a minimal effect on the regeneration of the zebrafish tail fin, in contrast to the strong inhibitory effect of the classical GC beclomethasone. The mechanism underlying the selective action of ginsenosides is still unclear. This action may result from a different conformation of the GR ligand-binding domain upon Rg1 binding. This conformation may preferentially recruit certain types of coregulator proteins and subsequently trigger the transrepression rather than the transactivation activity of GR.

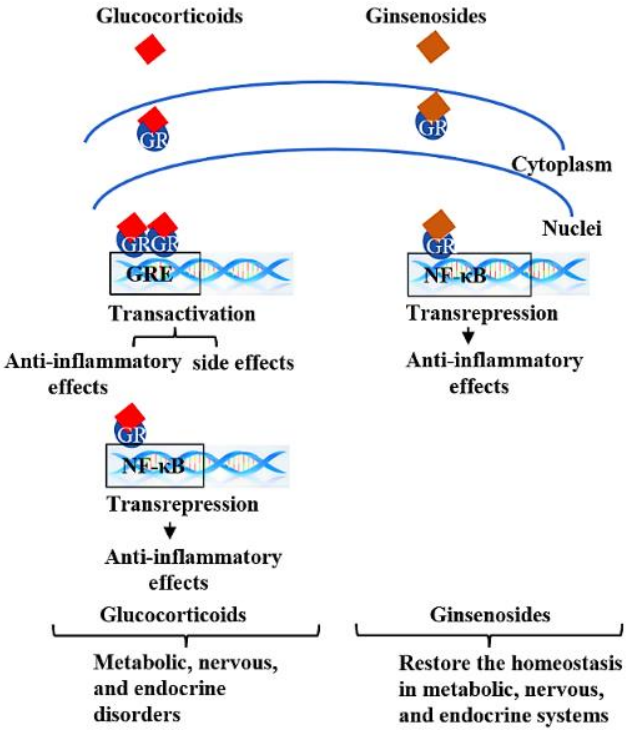


Figure 3. *Ginsenosides act as selective glucocorticoid receptor modulators, selectively inducing the transrepression activity of GR rather than its transactivation activity. As a result, ginsenosides mediate anti-inflammatory without triggering the side effects that classical glucocorticoids cause.*

Due to the selective action of ginsenosides on GR function, ginsenosides may also act as a selective antagonist, which may, when it is used as cotreatment, competitively antagonize certain GC-induced side effects. Therefore, the effects of ginsenosides in combination with classical GC has been studied as well (Li et al. 2014). For example, the effects of Rh1 in combination with dexamethasone were investigated in primary mouse hepatocytes. Ginsenoside Rh1 potentiated dexamethasone's anti-inflammatory effects. Rh1 improved the transrepression of NF-κB action by GR. Significantly, Rh1, in combination with dexamethasone, restored the expression of GR, while dexamethasone alone decreased the expression of GR. Importantly, Rh1 partly countered the transactivation of the GRE-driven genes gluconeogenic enzyme glucose-6-phosphatase (*G6P*) and phosphoenolpyruvate carboxykinase phosphatase (*PEPCK*). Therefore, Rh1 may counter the metabolic side effects triggered by GC treatment (Li et al. 2014). Another study demonstrated that treatment with ginsenoside Rg1 and low doses of GCs in RAW264.7 cells stimulated by LPS exerted significant anti-inflammatory effects. This combination decreased the production of NO and TNF-α more potently than introducing Rg1 or cortisone individually. Moreover, Rg1 combined with cortisone restored GR expression, while introducing cortisone alone reduced GR expression (Song et al. 2013). In agreement with these studies, it has been reported that ginsenosides partially reverse the dexamethasone-induced downregulation of GR in human hepatocyte (HL7702) cells (Ling et al. 2005).Collectively, we present

evidence that ginsenosides act as a selective GR agonist in *vitro* and in *vivo*, with potent anti-inflammatory effects but without triggering side effects. Therefore, understanding the mechanistic effects of ginsenosides will provide novel mechanistic insights which may lead to the development of improved anti-inflammatory GCs. In addition, these compounds may be used as selective antagonists in cotreatment with classical GCs, thereby reducing their side effects.

6. Conclusions

Suppression of inflammation and its signaling cascades is a recurring theme when understanding the pharmacological effects of ginsenosides in diseases. A major mechanism of action of ginsenosides is that they function as ligands of the GR, with the repression of genes involved in the immune response as a primary mechanism of action. We showed that ginsenosides act similarly to classical GCs, albeit with lower affinity for the GR, but with more selectivity. Due to the selective induction of the transrepression activity of the GR, in the absence of transactivation activity, ginsenosides display anti-inflammatory activity without triggering the severe side effects that would, for example, impair endocrine and metabolic balance or affect wound healing and tissue regeneration. The low bioavailability and absorption rate of ginsenosides and their low affinity for GR complicates their clinical application despite their potent pharmacology effects in certain disease models. However, unraveling the molecular mechanism underlying the selective GR activation by ginsenosides may open up a new avenue toward the development of novel anti-inflammatory GC drugs with reduced side effects.

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