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Review

Anti-inflammatory effects of ginsenosides from *Panax ginseng* and their structural analogs

Jongsun Park[1] and Jae Youl Cho[2]*

[1]College of Medicine, Chungnam University, Daejeon 301-131, Korea.
[2]School of Bioscience and Biotechnology and Institute of Bioscience and Biotechnology, Kangwon National University, Chuncheon 200-701, Korea.

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Ginsenosides (G) are biologically active saponin compounds found in *Panax ginseng*. Although these compounds are reported to possess numerous biological activities, recent issues have arisen regarding their immunosuppressive and anti-inflammatory roles in inflammatory cells. This is because 1) inflammation, managed by a large amount of different pro-inflammatory mediators such as cytokines, nitric oxide (NO) and prostaglandin (PG)E_2, is now considered as a principle cause of most immunological diseases, such as cancer and autoimmunity; and 2) some ginsenosides (e.g., G-Rb1, G-Rd and G-Rh2) can modulate these phenomena effectively by inhibiting the production of inflammatory mediators through suppressing the activation of nuclear factor (NF)-κB and its upstream signaling cascade. This review, therefore, discusses the *in vitro* and *in vivo* anti-inflammatory effects of ginsenosides in detail and proposes the possibility that ginsenosides, or their derivatives, can be developed as pharmaceutically useful drugs against NF-κB-mediated inflammatory diseases.

Key words: Ginseng saponin, ginsenoside, inflammation, tumor necrosis factor-α, nitric oxide, prostaglandin.

INTRODUCTION

The immune response is the most important defense mechanism for removing pathogens that have invaded a host. This response plays an important role in neutralizing, removing and destroying toxic materials, such as microorganisms, viruses and chemical components (Bermudez, 1994). The immune system is largely divided into 2 components; one being innate immunity and the other being adaptive immunity (Figure 1). Innate immunity participates in defending the host through

1) anatomic barriers such as the skin and mucosal surface,
2) physiologic barriers such as temperature, pH and chemical mediators (that is, lysozyme and collectin),
3) phagocytic/endocytic barriers to foreign organisms and materials,
4) finally resistance to infection through the inflammatory response (Naumann, 2000).

Adaptive immunity, as called acquired immunity, has 4 central characteristics: antigenic specificity, diversity, memory and self/non-self recognition (Medzhitov and Janeway, 1998). These include 2 different patterns of immune responses, the humoral immune response and the cell-mediated immune response, for removal of various foreign materials and microorganisms from the host (Medzhitov and Janeway, 1998). The humoral immune response is mediated mainly by B cell-produced antibodies, together with complement produced from hepatocytes or macrophages. On the other hand, the cell-mediated immune response is mediated by the cooperation of T helper cells (CD4+), cytotoxic T cells (CD8+), B cells, and antigen presenting cells.

Inflammation, an important component of innate immunity, occurs frequently in the host (Gordon, 1998). For example, for patients with a cold, macrophages and dendritic cells in the tonsil experience various inflammatory responses against infecting viruses and/or co-infecting bacteria. These include phagocytic uptake of virally- or bacterially-infected cells and subsequent activation of phagocytes such as macrophages, neutrophils and den-

*Corresponding author. E-mail: jaecho@kangwon.ac.kr. Tel.: +82-33-250-6562. Fax: +82-33-253-6560.

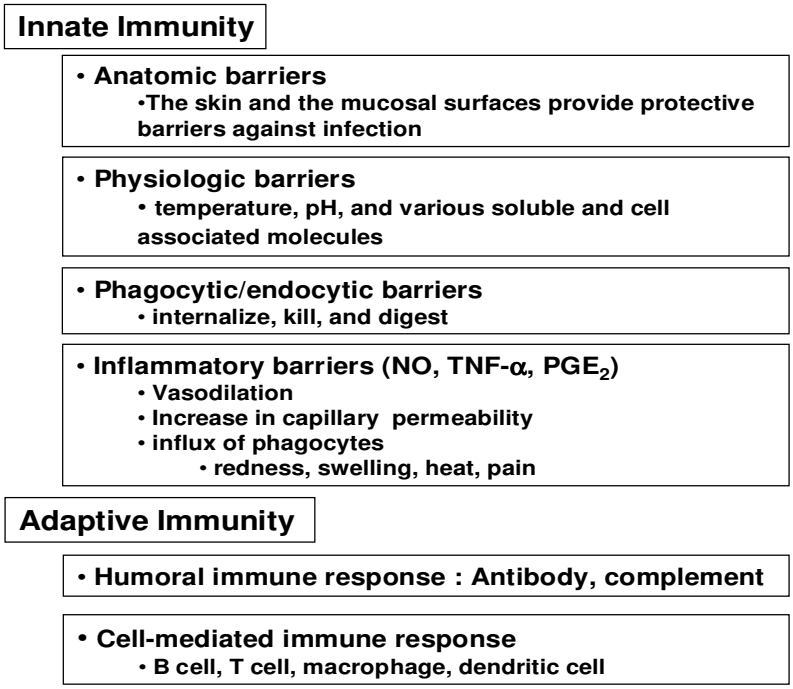

Figure 1. Two different types of immunity: innate immunity and adaptive immunity.

dritic cells. Furthermore, the release of cell wall products or viral proteins induces the activation of immune cells to boost overall inflammatory responses through production of numerous chemical mediators such as histamine, nitric oxide (NO), prostaglandins (PGE_2) and leukotrienes (Radi et al., 2001). These molecules also help leukocytes to migrate from the blood to inflamed tissue areas and also to secrete other pro-inflammatory cytokines (tumor necrosis factor [TNF]-α interleukin [IL]-1, IL-6) and chemokines (macrophage inflammatory protein 1α, IL-8, monocyte chemoattractant protein-1) (Sanchez-Madrid and Gonzalez-Amaro, 2001). These overall processes are expressed as redness, swelling, heating and pain, helping to disrupt and clear invading organisms through sustained activity. Several mediators of inflammation, such as PGE_2, NO and TNF-α and the enzymes that produce them (cyclooxygenase [COX] and NO synthase [NOS], etc.) play a critical role in regulating the complete immune response for the inflammation pathway, thus becoming an important research target for development of immunomodulatory drugs (Martel-Pelletier et al., 2003).

The inflammatory response is divided into 2 categories, acute inflammation and chronic inflammation, according to duration (Sanchez-Madrid and Gonzalez-Amaro, 2001). Acute inflammation is a general form of inflam-mation that continues for several days or weeks. On the other hand, chronic inflammation can be caused by acute inflammation of long duration, extending past four weeks. In the case of normal inflammation, cytokines produced by Th1 cells (IL-2, interferon [IFN]-γ, TNF-α, and so on) would soon be decreased by Th2 cells releasing IL-4, IL-6, IL-10 and transforming growth factor-β (Vervo-ordeldonk and Tak, 2002). Mutual balance between Th1 and Th2 responses in inflammation immediately atenuate acute inflammatory conditions back to normal (Levite and Chowers, 2001). Nonetheless, certain condi-tions with imbalanced Th1/Th2 responses lead to chronic inflammation states. These reactions are mainly managed by inflammatory cells that consist of monocytes, macrophages, lymphocytes and plasma cells (Maddox and Schwartz, 2002).

Ginseng, a perennial plant of Araiaceae, is a popular traditional herbal medicine and has been used since ancient times Ginseng has been known as the best medicine for increased vitality, long life, supplement of spirits and light bodies. The Chinese traditional medicine book, “Sin-Nong-Bon-Cho-Kyung,” written 2,000 years ago, states that “ginseng strengthens the 5 viscera, stabilizes spirit, fixes the soul, stops sudden palpitation, eliminates exogenous pathogen, sharpens visual and mental acuity and lightens the body” (Liu and Xiao, 1992). Regarding the different forms of ginseng, it has been shown that Korean ginseng (*Panax ginseng*) is one of the best, in terms of active components. The pharmacological effects of ginseng mainly originate from ginseng saponins, in particular ginsenosides (Hasegawa, 2004).

In regards to structure, ginsenosides are divided into 2 types, protopanaxadiol (PPD, 22 classes) and protopanaxatriol (PPT, 10 classes) (Table 1 and Figure 2). Numerous experimental investigations to better understand

Table 1. Two structural types of ginsenosides form *Panax ginseng*.

Protopanaxadiol	Protopanaxatriol
Ra1, Ra2, Ra3,	G-Rc, G-Rf,
Rb1, Ra2, Ra3,	G-Rg2, G-Rh1,
Rc, Rd	20-Glc-G-Rf
20(S)G-Ra3	Notoginsenoside-R1
20(R)G-Rg3	20(R)G-Rg2
Rh2, Rs1, Rs2	20(R)G-Rh1, Rh4
Quinqueno side-R1	
Notoginsenoside-R4	
Maylonyl-G-Rb1,	
Maylonyl-G-Rb2,	
Maylonyl-G-Rc,	
Maylonyl-G-Rd	

ginseng's pharmacological mode of action have been made. Owing to such efforts, pharmacological knowledge of ginseng components regarding cardiovascular disease, diabetes mellitus, cancer, stress and immunostimulation have been greatly explored (Hasegawa, 2004). In contrast, the immunosuppressive and anti-inflammatory effects of ginseng have not been fully elucidated. Therefore, in this review, the inflammation-related pharmacology of ginsenosides and their metabolites or derivatives will be summarized and discussed.

IN VITRO INHIBITION OF INFLAMMATORY MEDIATORS

For evaluating the inhibitory effect of ginsenosides on the production of inflammatory mediators, several *in vitro* model systems were employed. Thus, bacteria-derived inflammatory stimuli such as lipopolysaccharide (LPS) and peptidoglycan and macrophage-like cell lines such as J774 and RAW264.7 cells or primary macrophages prepared from peritoneal macrophages were used (Cho et al., 2001a; Hong et al., 2003; Kim and Cho, 2008). In particular, various inflammatory molecules, including TNF-α, NO (produced by inducible NOS [iNOS]) and PGE_2 (produced by COX-2), were measured as quantitative parameters (Cho et al., 2004; Lee et al., 2008, Byeon et al., 2008).

A representative cellular event induced by LPS is summarized in Figure 3. Thus, the activation of macrophages by LPS initially requires the molecular association of CD14 and toll-like receptor-4 to build signaling complexes including various protein kinases such as non-receptor type protein tyrosine kinases [e.g., c-Src and Janus kinase (JAK)-2)], protein kinase C and protein kinase A (Fujihara et al., 2003). The signaling activation is also linked to the stimulation of various enzymes such as nuclear factor (NF)-κB-inducing kinase (NIK), phosphoinositide 3-kinase (PI3K), phosphoinositide-dependent kinase 1 (PDK1), Akt (protein kinase B), mitogen activated protein kinases (MAPKs) [such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38] and anti-oxidative proteins like heme oxygenase (HO)-1 (Fujihara et al., 2003). These proteins play central roles in controlling several redox-sensitive transcription factors such as NF-κB, cAMP responsive element (CRE) and activator protein (AP)-1.

Inhibitory effect of TNF-α production

Cytotoxic T cells, natural killer cells, lymphocyte activated killer cells and activated macrophages destroy cancer cells, virus-infected cells and transplanted cells (Ortaldo, 1991). When immune cells attack their targets, various cytotoxic proteins such as lymphotoxin, TNF-α, NK cytotoxic factor, perforin, and toxic molecules such as NO and reactive oxygen species (ROS) (Sinkovics and Horvath, 2005) are typically involved. Most notably, TNF-α was originally characterized as a tumor-necrosis molecule, produced from macrophages, NK cells and T cells (Vujanovic, 2001). However, excessive TNF-α release during inflammation causes damage to normal tissues and cells, while further augmenting the production of other inflammatory molecules, leading to chronic conditions (Romas et al., 2002).

Indeed, elevated levels of TNF-α have been reported to be maintained in the blood or tissues of patients with chronic arthritis and septic shock (Glauser, 1996; Zanotti et al., 2002). For these reasons, anti-TNF-α therapy such as antagonistic small molecules, soluble TNF-α receptors and antibodies to TNF-α have been used for treatment of chronic or acute inflammatory diseases (Bluethmann et al., 1994). Concomitantly, significant efforts have been made to develop curative TNF-α-targeted drugs with anti-inflammatory and anti-autoimmunity properties (Pass et al., 1995).

We have previously reported that some ginsenosides help to regulate TNF-α release in LPS-treated macrophages (Cho et al., 2001b). As such, G-Re and G-Rg1 (PPT type ginsenosides) did not block TNF-α production. In contrast, PPD-type ginsenosides (G-Rb1 and G-Rb2) exhibited significant inhibition of TNF-α release with IC50 values of 48 and 27.9 μM, respectively (Table 2). Meanwhile, a mixture of protopanaxadiol-type saponins (100 to 200 μg/ml) also blocked other pro-inflammatory cytokines and chemokines such as IL-1β and MCP-1 at the transcriptional level, although the exact molecular mechanisms were not explored.

Ginsenosides are known to inhibit cAMP phosphodiesterase (PDE) (Stancheva and Alova, 1993). Indeed, combinatorial treatment of G-Rb1 or G-Rb2 with cAMP PDE inhibitors displayed no more additive effect on TNF-α release than single treatment with these drugs (Cho et

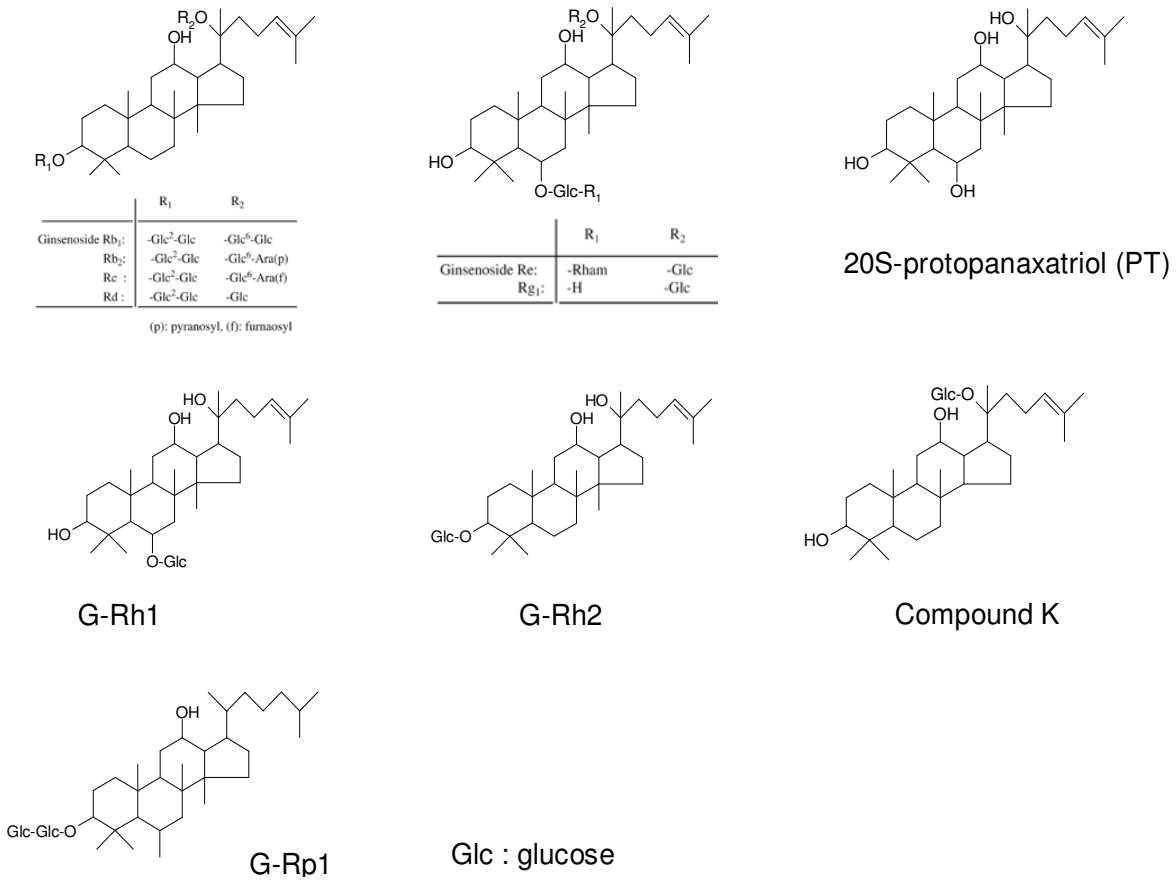

Figure 2. Chemical structures of ginsenosides.

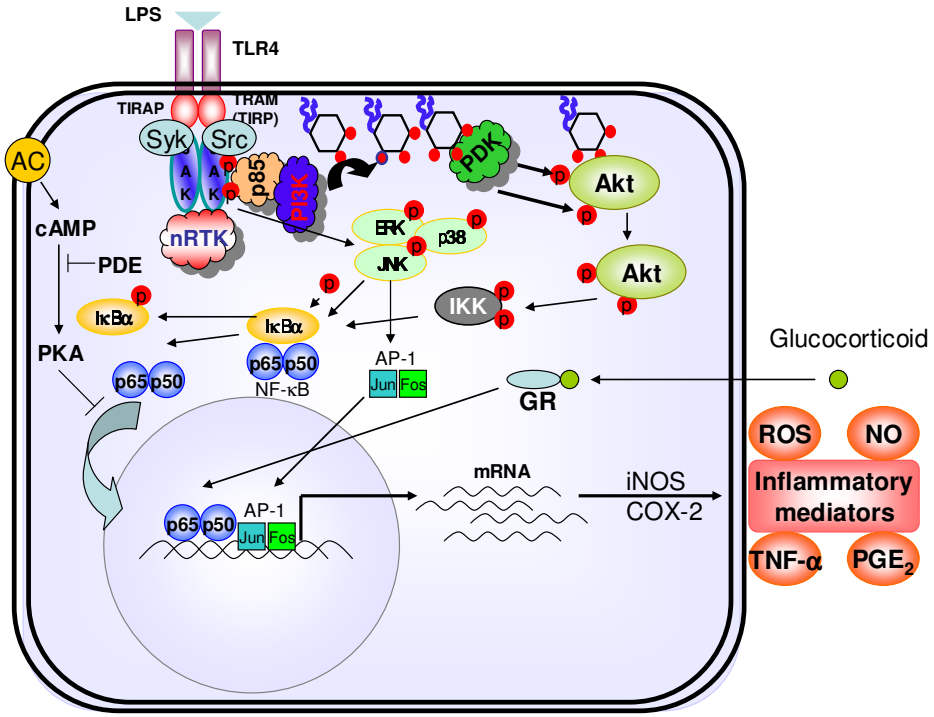

Figure 3. Signaling pathways involved in LPS-induced inflammatory responses.

Table 2. Inhibitory effect of ginsenosides on TNF-α production (Cho et al., 2001).

Compound	IC50 (μM)	
	RAW264.7	U937
PPD		
G-Rb1	56.5 ± 4.3	51.3 ± 2.1
G-Rb2	27.5 ± 2.5	26.8 ± 3.6
G-Rc	64.5 ± 4.3	
Positive control drug		
Pentoxifylline	252.4 ± 18.5	
Theophylline	526.3 ± 32.6	
dbcAMP	29.1 ± 3.7	46.7 ± 2.3
Prednisolone	33.6 ± 5.1	

al., 2001b). This implies that ginsenosides compete with selective cAMP inhibitors for the same enzyme binding site. In contrast, combined treatment of ginsenosides (G-Rb1 and G-Rb2) with inhibitors to protein kinase C (staurosporine and sphingosine), protein tyrosine kinases (herbimycin and genistein), or steroidal drugs (prednisolone and methyl-prednisolone) additively increased TNF-α inhibitory activity (Cho et al., 2001b). Particularly, no additive inhibition of combination treatment of G-Rb1 with selective PDF type IV inhibitors (rolipram and RP73401) strongly indicated that PDE type IV appears to be one of the pharmacologic targets of ginsenosides (Cho et al., 2001b). In agreement with this, PDE IV has been reported to be hyper-activated under inflammatory conditions and found to be highly expressed in inflammatory cells (Spina, 2003). Furthermore, combination experiments also suggested that co-treatment of ginsenosides with inhibitors to other enzymes (such as protein kinase C and protein tyrosine kinase) could enhance the curative effect of ginsenosides against TNF-α-mediated inflamma-tory diseases such as rheumatoid arthritis and septic shock (Cho et al., 2001b).

Strong apoptosis-inducing saponins, G-Rh1 and G-Rh2, which are main metabolites of G-Rg3 intestinally (Bae et al., 2002), are also known as inhibitors of pro-inflammatory TNF-α and IL-1β in LPS/IFN-γ-activated BV-2 cells, while increasing the expression of the anti-inflammatory cytokine IL-10 (Bae et al., 2006b). According to pharmacological and electrophoretic mobility shift assays, the prime targets of G-Rh2 were both the protein kinase A (PKA) pathway and the LPS/IFN-γ-induced DNA binding activity of AP-1, but not the cAMP responsive element binding protein or NF-κB.

A group from China has shown that PPT-type and PPD-type ginsenosides have different effects on the production of TNF-α by LPS-activated N9 microglial cells (Wu et al., 2007). Both PPT-type ginsenosides (G-Rg1 and G-Re) and PPD-type ginsenosides (G-Rb2 and G-Rd) inhibited LPS-induced TNF-α production via blocking the phosphorylation of ERK 1/2, JNK and c-Jun, as well as blocking NF-κB activation.

Inhibitory effect of NO and PGE_2 production

NO has multiple roles; acting as neurotransmitter, blood clotting molecule, blood pressure regulator and cancer cell attacker with non-carbonic and low molecular weight radicals (Shah et al., 2004). NO is synthesized from L-arginine by NOS (Chiarugi et al., 1998), which is divided into 2 groups: one is constitutive NOS (cNOS), which performs various physiological roles induced in the normal condition relevant to vascular functions, and the other is iNOS, which is induced under the pathologic condition (Shinoda and Whittle, 2001). Recently, iNOS has been regarded as a therapeutic target in many immunologic disorders, because it is a pro-inflammatory enzyme highly expressed in activated macrophages and microglia by various immunological or pathological stimuli such as LPS or IFN-γ (MacMicking et al., 1997). Large amounts of NO produced in inflammatory cells expose a host to serious damage via its chemical reactivity (Alexander, 1998) and also stimulate the production of other inflammatory mediators such as PGE_2 produced by COX-2 (Murakami and Ohigashi, 2007). A critical role of NO has also been demonstrated in a septic shock model in which iNOS was highly expressed in Kupffer cells and hepatocytes from sepsis patients (Kirkeboen and Strand, 1999).

Strong apoptosis-inducing saponins, G-Rh1 and G-Rh2, are also known as effective NO synthesis inhibitors (Park et al., 1996; Bae et al., 2006b). Thus, these compounds strongly suppress NO production induced by IFN-γ plus LPS in murine peritoneal macrophages. Unlike TNF-α inhibitory effects, PPD-type (G-Rb1, G-Rc or G-Re) ginsenosides did not inhibit NO release. In addition, IFN-γ-induced early signaling for boosting NO production induced by LPS appears to be regarded as the molecular target of G-Rh1 and G-Rh2. This is because treatment of the cells with G-Rh2 6 h before stimulation with IFN-γ plus LPS showed more inhibitory effect than treatment with G-Rh2 6 h after or simultaneously with IFN-γ plus LPS for NO production.

Prof. Kim's group in Kyung Hee University (Seoul, Korea) also proved the anti-inflammatory effect of G-Rg3 and G-Rh2 using LPS- and IFN-γ-induced murine BV-2 microglial cells. It was found that G-Rh2 is able to suppress the production of NO, with an IC50 value of 17 μM. Blockade of iNOS mRNA levels induced by LPS also indicated that the inhibitory effect of Rh2 occurred at the transcriptional level. Additionally, G-Rh2 was found to inhibit the expression of COX-2. In view of this, the G-Rg3-induced preventive effect against LPS-induced hepatic and renal injury in rats treated at a dose of 10 mg/kg body weight/day seems to be due to its metabolite, G-Rh2 (Kang et al., 2007). In G-Rg3-treated liver and kidney, most of inflammatory parameters such as NF-κB, iNOS and COX-2 were reduced, while the anti-inflammatory protein, HO-1, was up-regulated. In addition, NO

produced in LPS-activated N9 microglial cells was down-regulated by protopanaxatriol-type G-Rg1 and G-Re by blocking NF-κB activation (Wu et al., 2007).

As an additional example drug, G-Rd has neuroprotective effects based on its anti-inflammatory action (Lin et al., 2007). A reduction of NO-formation and PGE_2 synthesis was also observed in G-Rd-treated mesencephalic primary cultures. Thus, the protective mechanism of G-Rd is thought to interrupt iNOS and COX-2 expression.

Recently, 20(S)-protopanaxatriol (PT), one of glycones of ginsenosides, was found in human blood as a final metabolite after oral administration of ginseng extract (Hasegawa et al., 1997) and demonstrated anticancer activity (Shibata, 2001). Interestingly, this glycone was reported to inhibit the expression of iNOS and COX-2 in LPS-stimulated macrophages, at concentrations from 0 to 20 μM (Oh et al., 2004). When macrophage-like RAW-264.7 cells stimulated with LPS were treated with PT, NO production and iNOS expression were dose-dependently repressed, up to 20 μM of PT, without altering cell viability (Oh et al., 2004). The compound also inhibited PGE_2 production and COX-2 expression in a dose-dependent manner (Oh et al., 2004). The inhibition of iNOS and COX-2 expression by PT was mediated by blocking nuclear translocation of NF-κB (Oh et al., 2004; Cho et al., 2008). Although the exact inhibitory mechanisms of PT have not been fully explained, a series of NF-κB activation pathways, such as the phosphorylation of IκBα, an inhibitor of the NF-κB (p65/p50) activation and the activation of IκB kinase (IKK) (Figure 2) seems to be considered as a potential target of PT action (Oh et al., 2004; Cho et al., 2008). In contrast, considering that RU486, an antagonist of the glucocorticoid receptor, did not abrogate the inhibitory effect of PT (Figure 2), the anti-inflammatory effect of PT seems to be mediated in a glucocorticoid receptor-independent manner (Oh et al., 2004). Professor Kim's group in Kyung Hee University had also reported that 20-O-β-D-glucopyranosyk-20(S)-protopanaxadiol (compound K) (5~25 μM) is able to block LPS-induced production of NO and PGE_2 in macrophages (Park et al., 2005). The expression of iNOS and COX-2 was also suppressed by compound K treatment (Park et al., 2005). Similar to PT, this compound has been found to diminish the activation of NF-κB (Park et al., 2005).

THERAPEUTIC *IN VIVO* EFFECT IN INFLAMMATORY MODELS

So far, animal models have widely been employed to evaluate the curative effects of anti-inflammatory candidate drugs. Acute or chronic mouse and rat models are generally used after treatment with various inflammatory stimuli such as croton oil, carageenan, arachidonic acid and collagen (Cho et al., 2001a; Deschoolmeester and Else, 2002). In these models, inflammatory mediators such as histamine and prostaglandins are found to play a critical role in managing various acute or chronic inflammatory symptoms (Cho et al., 2001a). Acute inflammation models frequently used include septic shock, induced by gram negative bacteria-derived endotoxins like LPS, which produce significant TNF-α and NO secretion, as well as ear edema methods, induced by croton oil and arachidonic acid (Cho et al., 2000). Arthritis models induced by adjuvant containing type II collagen or Mycobacteria to induce edema in joint areas for longer periods are popular as a chronic inflammation model (Cho et al., 2004). In addition, a dermatitis model, involving treatment with a stimulus that induces chronic dermatitis, like psoriasis, has also been used for determining the pharmacological efficacy of anti-inflammatory candidate drugs (Shin et al., 2005).

The *in vivo* curative effects of components derived from Korean ginseng in inflammatory diseases by have been less reported compared to other natural products. Nevertheless, therapeutic effects of ginseng ingredients have been proven against chronic dermatitis (such as psoriasis and contact dermatitis) and rheumatoid arthritis models. Shin et al. (2005) has reported that Rb1 and compound K were effective in a mouse model of psoriasis, a cutaneous skin inflammatory disease with red and flat lesions of various size and silver-white tone's thick stratum corneum, induced by oxazolone (Shin et al., 2005). Although this is known as a type of delayed hypersensitive reaction managed by Th1 cells, most pathological symptoms are similar to those of chronic inflammatory skin dermatitis. Indeed, Rb1 and compound K (0.02 and 0.05%) normalized the increased thickness level of the ear as a result of oxazolone-induced inflammatory mediators (Shin et al., 2005).

Recently, the anti-inflammatory effect of steamed red ginseng, as well as ginseng, is being explored (Bae et al., 2006a). Bae et al. (2006) reported that components (G-Rg3, G-Rf and G-Rh2) found in steamed red ginseng blocked inflammatory responses both in a passive cutaneous anaphylaxis (PCA) reaction and contact dermatitis (Bae et al., 2006a). The PCA model is a cutaneous inflammatory disease with allergic shock, generated by injected anti-dinitrophenol (DNP)-IgE and antigen and DNP-human serum albumin (Ovary, 1982). The orally administered Korean red ginseng saponin fraction (KRGS) has been found to dose-dependently repress the PCA model; 32% in 100 mg/kg, 61% in 500 mg/kg (Bae et al., 2006a). Oral and i.p. treated ginsenosides, such as G-Rg3, G-Rf and G-Rh2, displayed an inhibitory tendency with 30 to 60% inhibition (Bae et al., 2006a). Furthermore, these components, as well as KRGS, also diminished ear swelling in an ear dermatitis mouse model induced with oxazolone. By histopathological analysis, 0.05% of G-Rf, G-Rg3 and G-Rh2 repressed ear swelling more than the control drug, betamethasone, by up to 34.8, 47.5 and 49.9%, respectively (Bae et al., 2006a).

Rheumatoid arthritis (RA) is a chronic inflammatory

Table 3. Summary of ginsenoside-mediated *in vitro* anti-inflammatory action.

Ginsenoside	TNF-α	NO	iNOS	PGE_2	COX-2	Molecular target	References
G-Rb1	+ (RAW)					cAMP PDE	Cho et al., 2001b Oark et al., 2005
G-Rb2	+ (RAW) + (N9)					cAMP PDE	Cho et al., 2001b
G-Rh1	+ (BV2)	+ (PM)					Park et al., 1996
G-Rh2	+ (BV2)	+ (PM) + (BV2)	+ (BV2)	+ (BV2)	+ (BV2)	PKA, AP-1	Park et al., 1996
G-Rg1	+ (N9)	+ (N9)				ERK, JNK, NF-κB cAMP PDE	Stancheva and Alova, 1993, Wu et al., 2007
G-Re	+ (N9)	+ (N9)				ERK, JNK, NF-κB	Wu et al., 2007
G-Rg3		+ (BV2)					Bae et al., 2006b Kang et al., 2007
G-Rd		+ (MP)		+ (RAW)			Lin et al., 2007
PT		+ (RAW)	+ (RAW)	+ (RAW)	+ (RAW)	NF-κB	Choo et al., 2008 Oh et al., 2004
Compound K		+ (RAW)	+ (RAW)	+ (RAW)	+ (RAW)		Park et al., 2005

+: Inhibitory effect; RAW: RAW264.7; PM: peripheral Macrophage; MP: mesencephalic primary; BV2: BV2 microglial cells; N9: N9 microglial cells.

disease with complicated immunopathology (Lorenz et al., 2001). In particular, two proinflammatory cytokines, TNF-α and IL-1β are secreted chronically from activated macrophages or dendritic cells and are known to be major causes of disease onset (Freeman and Buchman, 2001; Lorenz, 2000). Although the exact pathophysiological mechanisms are not yet fully understood, these cytokines are reported to play critical roles in stimulating proteolytic enzymes, such as matrix metalloproteinases (MMP), involved in direct destruction of articulation (Burrage et al., 2006). According to a report published by Kim et al. (2007), G-Rb1 clearly inhibited edema formation in the joint, as well as expression of TNF-α derived from chondrocytes in a collagen-induced RA model (Kim et al., 2007). The inhibitory effect of TNF-α by G-Rb1 has also been proven in TNF-α secretion from peripheral blood mononuclear cells (PBMC) following LPS or IFN-α stimulation as well as RAW264.7 cells (Kim et al., 2007; Cho et al., 2001b). These results suggest that G-Rb1 can be regarded as the most potent medication currently available for the treatment of rheumatoid arthritis.

ANTI-INFLAMMATORY EFFECT OF NOVEL GINSENOSIDE DERIVATIVES

Development of biologically-active ginsenosides for medicinal purposes is, in fact, limited and unqualified for patent status, since the components are widely known. To overcome this limitation, a new approach to develop novel ginsenoside-originated compounds with improved pharmacological activity is required. Recently, our group attempted to develop novel ginsenoside derivatives by means of a reduction with hydrogenation. As a result, G-Rp1 (Figure 2) was prepared on a large scale from a crude ginsenoside mixture (e.g., G-Rg5 and G-Rk1) and was found to be immunopharmacologically active. Thus, this novel derivative displayed stronger anti-inflammatory and anti-cancer activities than other ginsenosides such as G-Rg3. G-Rp2 dose-dependently diminished NO production, TNF-α secretion and IL-1β release in LPS-activated macrophages (Kim et al., 2008, In revision). G-Rp1-mediated inhibition of inflammatory mediators appears to be due to suppressing IκBα phosphorylation and NF-κB activation as in the case of other ginsenosides and their metabolites.

Conclusion

The most interesting points regarding ginseng and the immune system concern its immunostimulatory, anti-cancer and anti-oxidative activities. Recently, however, few researchers have investigated the possibility that ginsenosides could be also applied to anti-inflammatory diseases by exploring their *in vivo* and *in vitro* inhibitory mechanisms on inflammatory responses (summarized in Table 3 and Figure 4). For example, G-Rb1 and G-Rb2, of the PPD class, blocked TNF-α-production as well, as the release of NO and PGE_2, via repression of NF-κB activation signals. Indeed, due to these pharmacologic merits, it has been proposed that G-Rb1 could be developed as a new anti-arthritis drug. In addition, the fact that chemically converted ginsenoside components such as compound K, intestinal microorganism-derived G-Rb1 metabolites and steamed red ginseng extracts

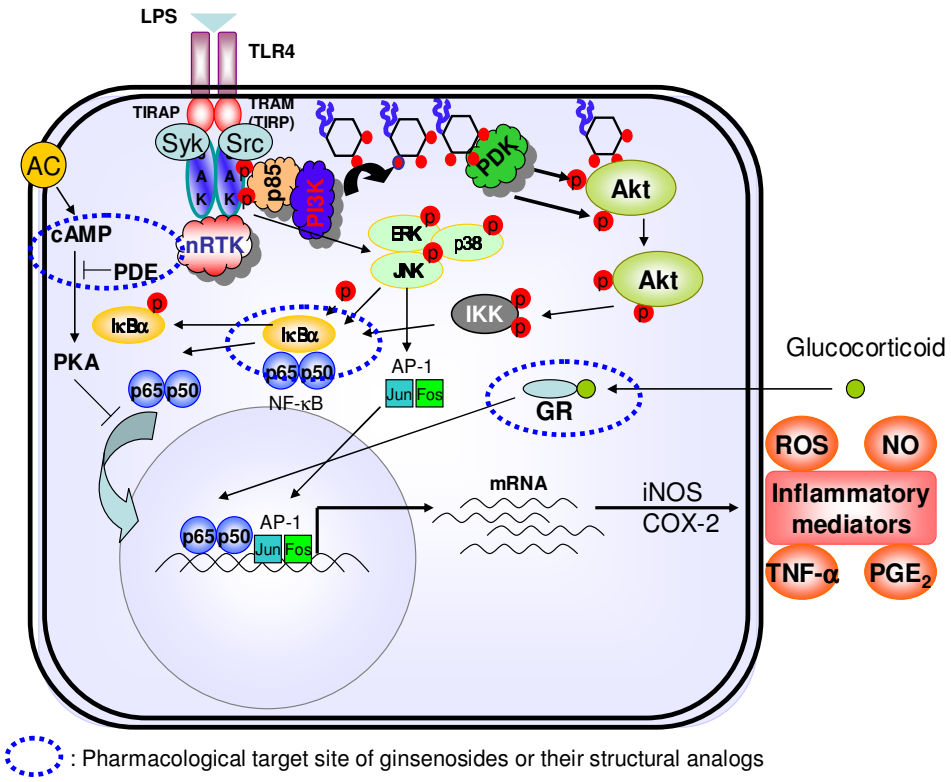

Figure 4. Pharmacological targets of ginsenosides or their structural analogs in inflammatory responses.

inhibited *in vitro* anti-inflammatory activities as well as delayed hyper-sensitive dermatitis seem to emphasize the functional importance of ginseng metabolites in regard to future research. Indeed, new derivatives such as G-Rp1, pre-pared by various chemical processing and fermentation technologies, are now actively studied. Therefore, it is anticipated that newly prepared active saponin metabolites, or their modified structures, with strong and safe immunosuppressive and anti-inflammatory properties will be developed in the near future.

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