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Review

Effects of *Panax ginseng* on Tumor Necrosis Factor-α-Mediated Inflammation: A Mini-Review

Davy CW Lee [1,*] and Allan SY Lau [1,2,*]

[1] Cytokine Biology Group, Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

[2] Molecular Chinese Medicine Laboratory, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China

* Authors to whom correspondence should be addressed; E-Mails: dcwlee@hku.hk (D.C.W.L.); asylau@hku.hk (A.S.Y.L.); Tel.: +852-2255-4269; Fax: +852-2855-1523.

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Abstract: *Panax ginseng* is one of the most commonly used Chinese medicines in China, Asia and Western countries. The beneficial effects of ginseng have been attributed to the biological activities of its constituents, the ginsenosides. In this review, we summarize recent publications on the anti-inflammatory effects of ginseng extracts and ginsenosides on cellular responses triggered by different inducers including endotoxin, tumor necrosis factor-alpha (TNF-α), interferon-gamma and other stimuli. Proinflammatory cytokines, chemokines, adhesion molecules and mediators of inflammation including inducible nitric oxide synthase, cyclooxygenase-2 and nitric oxide orchestrate the inflammatory response. Ginseng extracts and ginsenosides including Rb_1, Rd, Rg_1, Rg_3, Rh_1, Rh_2, Rh_3 and Rp_1 have been reported to have anti-inflammatory properties in different studies related to inflammation. Ginsenosides inhibit different inducers-activated signaling protein kinases and transcription factor nuclear factor-kappaB leading to decreases in the production of cytokines and mediators of inflammation. The therapeutic potential of ginseng on TNF-α-mediated inflammatory diseases is also discussed. Taken together, this summary provides evidences for the anti-inflammatory effects of ginseng extracts and ginsenosides as well as the underlying mechanisms of their effects on inflammatory diseases.

Keywords: *Panax ginseng*; ginsenosides; cytokines; immunomodulation; inflammation

1. Introduction

Panax ginseng C.A. Meyer (ginseng) was first classified by German botanist Nees Von Esenbeck in 1833. It was later renamed by Russian botanist Carl Anton Meyer in 1843 [1]. The name of the genus *Panax* was derived from a Greek word which literally means all-healing or panacea. [2]. Ginseng has been used as an herbal remedy in ancient China, Korea, Japan and the Far East for more than 5,000 years and the medical efficacy of ginseng was documented in ancient Asian literatures [1,3]. Following studies of the uses of ginseng in humans, the beneficial effects of ginseng were recognized in Western countries by the 18th century [4].

Ginseng belongs to the family *Araliaceae*. Currently, twelve to thirteen species of ginseng have been identified in the genus *Panax* and their geographical distributions are summarized in a recent review [1,3]. Three major species of ginseng including *Panax ginseng* C. A. Meyer, *Panax quinquefolium* L and *Panax notoginseng* have been extensively investigated for their physiological and pharmacological effects on the human body [5-7].

2. Active Components of *Panax ginseng*

Ginseng species contain multiple active constituents including ginsenosides, polysaccharides, peptides, phytosterols, polyacetylenes, polyacetylenic alcohols and fatty acids that have been shown to have different effects on carbohydrate and lipid metabolism, cognition and angiogenesis as well as on the function of neuroendocrine, immune, cardiovascular and central nervous systems [2,4].

The ginsenosides are the major biologically active compounds of ginseng. Recent studies have shown that ginsenosides play important roles in the pharmacological effects of ginseng [3]. Structurally, ginsenosides belong to the triterpene dammarane-type saponins and comprise triterpenoidal glycosides of the dammar type with glucose, arabinose, xylose or rhamnose [8]. Over 30 different ginsenosides have been isolated from ginseng and identified [3]. Twenty-two subtypes of ginsenosides including Ra_1 Ra_2, Ra_3 Rb_1, Rb_2, Rb_3, Rc, Rd, Rg_3 and Rh_2 belong to the 20(*S*)-protopanaxadiol group, whereas eleven subtypes of ginsenosides including Re, Rf, Rg_1, Rg_2 and Rh_1 belong to the 20(*S*)-protopanaxatriol group. Additionally, the oleanolic acid group contains ginsenoside Ro [2,9]. However, the concentration and bioactivities of ginsenosides in different ginsengs could vary by up to 20% [3]. The variability is related to the species, the part of the plant, the period of cultivation, and the processing method used [9,10]. Different pharmacological effects of ginsenosides have been reported and different combination of ginsenosides including 20(*S*)-protopanaxadiol and 20(*S*)-protopanaxatriols have been used in treating inflammatory diseases [11]. Moreover, ginseng contains other compounds including phenolic compounds, polyacetylenes, ginsenoyne, sesquiterpenes, methoxypyrazine, alkylpyrazine derivatives, sesquiterpene alcohols, panasinsanols, β-caboline, and neutral or acidic polysaccharides [8,10].

3. Inflammation and Cytokines

Inflammation is a complex biological response of our body to harmful external stimuli including microbial infections and chemical toxins. The inflammatory response is characterized by several steps including coordinate activation of signaling pathways, expression of proinflammatory cytokines,

chemokines and adhesion molecules in resident tissue cells, as well as infiltration of leukocytes mainly macrophages, neutrophils and dendritic cells and mediators of inflammation from the vascular system to remove the harmful stimuli and to initiate the healing process [12,13].

Leukocytes or endothelial cells produce proinflammatory or anti-inflammatory cytokines depending on their activities on regulating inflammation. Proinflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) have been shown to play central roles in the pathogenesis of both acute and chronic inflammatory diseases [14,15]. Other proinflammatory cytokines include IL-17, IL-18 and the newly identified member of IL-1 family, IL-33, whereas anti-inflammatory cytokines including IL-10 and transforming growth factor-β negatively regulate or dampen the over-activated inflammatory responses [16-25].

TNF-α plays critical roles in the initiation and amplification of inflammatory response [26-29]. TNF-α signaling pathways are triggered by binding of TNF-α to one of the two distinct cell surface receptors, TNF-R1 and TNF-R2. TNF-R1 mediates largely the proinflammatory and apoptotic pathways activated by TNF-α, whereas TNF-R2 is associated with TNF-mediated tissue repair and angiogenesis. Following binding of TNF-α to TNF-R1, downstream signaling pathways are triggered by the recruitment of cytosolic adaptor proteins including receptor interacting protein, TNFR associated factor2, and FAS-associated death domain through specific protein-protein interaction domains. The protein signaling complexes recruit distinct enzymes resulting in the activation of different signaling pathways including caspases, the transcription factor nuclear factor-kappaB (NF-κB) and mitogen activated protein kinases (MAPK), and eventually induced transcription of inflammatory mediators [28].

4. Anti-Inflammatory Effects of Ginseng Extracts and Ginsenosides

Ginseng extracts and the ginsenosides have been shown a wide range of beneficial effects against human diseases and their potential therapeutic effects have been attributed to its immunomodulatory, anti-oxidant and anti-inflammatory activities [30]. The anti-inflammatory effects of ginseng extracts and ginsenosides are associated with their properties of cytokine regulation and phagocytosis in innate immunity, as well as activation of T- and B- lymphocytes [31-36]. Moreover, reports have shown their adjuvant activities for different kinds of vaccines [9,37]. Previous reports of anti-inflammatory effects of ginseng extracts and ginsenosides will be described in following sections.

4.1. Panax ginseng Extract

Ginsan, the acid polysaccharide extract from ginseng, has been shown to have immunomodulatory effects in various reports. Ginsan inhibits the production of TNF-α, IL-1β, IL-6, IL-12, IL-18 and interferon-gamma (IFN-γ), and enhances the phagocytic activity of macrophages in *Staphylococcus aureus*-infected mice [38,39]. In addition, ginsan inhibits the activation of MAPK pathways including p38MAPK and c-Jun N-terminal kinases (JNK), and NF-κB in the infected mice [38]. Furthermore, ginsan is shown to have anti-asthmatic effects including reduction of airway hyperresponsiveness, and decreases of eosinophils in ovalbumin-treated mice. These effects are equivalent to those of dexamethasone treatment and could be partially mediated by enhancing the synthesis of cyclooxygenases and prostaglandin $(PGE)_2$ [40].

Ginsan exerts protective effects on mice with carbon tetrachloride-induced liver injury via inhibition of carbon tetrachloride-induced cytochrome P450 pathways and lipid peroxidation. In addition, ginsan attenuates the production of proinflammatory cytokines including IL-1β, IFN-γ and chemokines including monocyte chemoattractant protein (MCP)-1/CCL-2, macrophage inflammatory protein (MIP)-2β/CXCL-2 and KC/CXCL-1 leading to reduce leukocyte infiltration and inflammatory response [41]. However, ginsan stimulates the expression of IL-12, TNF-α and Major Histocompatibility Complex (MHC) class II molecules in murine dendritic cells and the proliferation of allogeneic CD4(+) T lymphocytes [42].

4.2. Panax Notoginseng Extracts

The anti-atherosclerotic and anti-arthritic effects of *Panax notoginseng* saponins (PNS) in rodents have been reported recently. PNS show anti-atherosclerotic effects on apolipoprotein E-deficient mice. The levels of serum lipid, IL-6 and TNF-α in PNS-treated mice are lower than those of control mice. The anti-atherosclerotic effects of PNS could be due to the inhibition of TNF-α induced monocyte adhesion and the expression of endothelial adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) [7]. In addition, PNS is shown to attenuate the pathological changes of atherosclerosis induced by zymosan A in rat. The expression levels of integrins, IL-18, IL-1β, matrix metalloproteinase-2 (MMP-2), MMP-9, and NF-κB are decreased in PNS-treated rats [6]. On the other hand, PNS attenuates the degree of hepatic fibrosis in mice treated with carbon tetrachloride. The levels of serum transforming growth factor-β1, TNF-α and IL-6 decrease in PNS-treated mice compared with the control mice whereas the level of IL-10 increases, suggesting that PNS has certain therapeutic effects on hepatic fibrosis by regulating the imbalance of pro-fibrotic and anti-fibrotic cytokines [43]. BT-201, n-butanol extract of *Panax notoginseng*, has been shown the anti-arthritic effects on collagen-induced arthritis (CIA) mice [5]. BT-201 also decreases the production of TNF-α, IL-1β, inducible nitric oxide, and MMP-13, possibly via the suppression of NF-κB, ERK, p38 MAPK and JNK activation [5]. Moreover, the ethanol extract of *Panax notoginseng* roots inhibits the expressions of TNF-α, IL-6 and CD40 in DC2.4 murine dendritic cells stimulated by Toll-like receptor ligands including lipopolysachharide (LPS), CpG and/or polyriboinosinic-polyribocytidylic acid [poly(I:C)]. However, the underlying mechanisms of the anti-inflammatory effects of *Panax notoginseng* extracts remains investigated [44].

4.3. Panax Quinquefolius Extracts

The ethanol extract of *Panax quinquefolius* selectively inhibits the expression of iNOS in RAW264.7 cells induced by LPS by suppressing the Signal Transducers and Activators of Transcription protein (STAT)/iNOS signaling pathways [45]. Another report shows that the ethanol extracts of *Panax quinquefolius* can suppress the expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2) and p53 in mice with experimental colitis. The mucosal and DNA damage associated with colitis in these mice are also suppressed by the *Panax quinquefolius* extract [46].

4.4. Rb_1

Ginsenoside Rb_1 inhibits the over-expression of VCAM-1 and over-production of superoxide anion in TNF-α treated endothelial cells by suppressing MAPK and NF-κB signaling pathways [47]. Rb_1 also inhibits the productions of inflammatory mediators including IL-8 and PGE_2 in HaCaT human keratinocytes induced by capsaicin [48]. Rb_1 inhibits capsaicin-induced calcium influx and NF-κB activity through capsaicin receptor also known as transient receptor potential channel vanilloid subtype 1 signaling pathways [48].

The anti-arthritic effect of Rb_1 has been reported in collagen-induced arthritis CIA mice. Rb_1 inhibits TNF-α induction in peripheral blood mononuclear cells, fibroblast-like synoviocytes, and chondrocytes stimulated by IFN-γ, LPS or IL-1β. In addition, Rb1 suppresses the severity of inflammatory response in CIA mice by reducing TNF-α expression, cartilage destruction and cell infiltration in the arthritic joints of the mice [49].

4.5. Rd

Ginsenoside Rd has been shown neuroprotective effects on a rat model of transient focal cerebral ischemia. Rd reduces the accumulation of the early detected oxidative DNA, protein and lipid peroxidation products in rats subjected to transient middle cerebral artery occlusion. Rd suppresses the inflammatory responses by inhibiting expressions of iNOS and COX-2 and microglial activation [50].

4.6. Rg_1

Ginsenoside Rg_1 inhibits the expression of TNF-α, iNOS and ionized calcium binding adaptor molecule-1 in both cerebral cortex and hippocampus in mice intracerebroventricular injected of LPS by suppressing NF-κB and MAPK pathways [51]. Consistent report shows that Rg_1 suppresses NF-κB pathways leading to decrease production of TNF-α and nitric oxide in N9 microglial cells induced by LPS. Rg_1 can be a potent inhibitor of microglial cells activation-mediated neuro-degenerative diseases [52]. On the other hand, Rg_1 induces Th1 dominant cytokines production such as IFN-γ and IL-2 in CD4(+) T cells of mice infected with *Candida albicans*. Such activities help the host to resist the risk of dissemination of candidiasis [53].

4.7. Rg_3

Ginsenoside Rg_3 inhibits the COX-2 expression as well as NF-κB and activator protein-1 activations in 12-O-tetradecanoylphorbol-13-acetate-induced mouse skin and human promyelocytic leukemia cells [54]. Rg_3 also reduces TNF-α, IL-1β, IL-6, MCP-1, MIP-1γ expressions in BV-2 murine microglial cells treated with beta-amyloid, indicating that Rg_3 prevents neurotoxicity by inhibiting proinflammatory cytokines production in microglial cells [55]. Rg_3 may have anti-atherosclerotic activities in the vasculature. Rg_3 suppresses the expressions of TNF-α induced VCAM-1 and ICAM-1 in ECV 304 human endothelial cells and prevents the endothelial cells undergo apoptosis through the Akt-mediated, caspases-activated pathways [56,57].

4.8. Rh_1

Ginsenoside Rh_1 may provide beneficial effects on neuroinflammatory diseases by modulating the microglial activation. Rh_1 suppresses production of nitric oxide, reactive oxygen species and TNF-α in BV2 microglial cells induced by IFN-γ. The study for iNOS promoter shows that IFN-γ-activated JAK/STAT and ERK signaling pathways, and their downstream transcription factors including NF-κB, interferon regulatory factor-1 and STAT1 was inhibited by Rh_1 [58]. In addition, Rh_1 induces expressions of IL-10 and hemeoxygenase-1 expression via activation of cAMP-dependent protein kinase signaling pathways. On the other hand, Rh_1 inhibits activation of NF-κB and extracellular signal regulated kinase (ERK1/2) signaling pathways and expressions of iNOS and COX-2 in LPS-stimulated microglia [59]. Hence, the anti-inflammatory effects of Rh_1 alleviate the severity of neuro-degenerative diseases.

A recent report shows that Rh_1 can alleviate inflammatory symptoms in oxazolone-induced atopic dermatitis-like skin lesions in hairless mice by suppressing the level of IgE and IL-6 in peripheral blood [60]. Additionally, Rh_1 reduces histamine release in rat peritoneal mast cells and the IgE-mediated passive cutaneous anaphylaxis reaction in mice [61]. The anti-allergic effects of Rh_1 may due to anti-inflammatory activities since Rh_1 inhibits the expression of iNOS and COX-2 in LPS-induced RAW264.7 murine macrophages by preventing phosphorylation and degradation of the inhibitor of NF-κB (I-κB) [61,62].

4.9. Rh_2 and Rh_3

Ginsenoside Rh_2 has specific inhibitory effects on activation of NF-κB and JNK signaling pathways in human astroglial cells-induced by TNF-α [63]. In addition, Rh_2 inhibits the DNA binding activity of activator protein 1 (AP-1) and production of nitric oxide, COX-2, TNF-α and IL-1β in BV2 cells induced by LPS and IFN-γ. On the other hand, Rh_2 can increase the expression of IL-10 in BV2 cells [64]. Ginsenosides Rh_2 and Rh_3 significantly inhibit LPS-induced microglial cells activation by suppressing expression of inflammatory mediators including iNOS, MMP-9, TNF-α, and IL-1β [65].

4.10. Rp_1

Ginsenoside Rp_1 is a newly reported ginsenoside derivative that show inhibitory effects on IL-1β expression in LPS-treated RAW264.7 cells by blocking the activation of NF-κB signaling pathways [66]. Our recent report demonstrated that the ethanol extract of *Panax ginseng* inhibits expressions of TNF-α-inducible cytokines and signaling proteins in human promonocytic cells. Ginseng extract suppresses TNF-α-induced chemokine CXCL-10 expression by inactivating the ERK1/2 pathway. We also showed that the suppressive effect of ginseng extract on TNF-α induced-CXCL-10 transcription could be due to the collective effects of ginsenosides mixtures instead of a single ginsenoside [67]. The inflammatory study models, targeted regulatory proteins and effects on inflammatory mediators for ginseng extracts and ginsenosides are summarized in Table 1.

Table 1. Summary of anti-inflammatory effects of ginseng extracts and ginsenosides.

Ginseng extract/Ginsenoside	Experimental model	Regulatory proteins	Effects on inflammatory mediators	References
Panax ginseng acid polysaccharide extract	Ovalbumin-treated mice	-	↓ Cyclooxygenases, PGE2	[40]
Panax ginseng acid polysaccharide extract	*Staphylococcus aureus*-infected mice	p38MAPK, JNK and NF-κB	↓ IL-1β, IL-6, IL-12, IL-18, IFN-γ	[38,39]
Panax ginseng acid polysaccharide extract	Carbon tetrachloride-induced mice	-	↓ CCL-2, CXCL-2, CXCL-1	[41]
Panax ginseng acid polysaccharide extract	Murine dendritic cells	-	↑ IL-12, TNF-α, MHC-II	[42]
Panax ginseng ethanol extract	TNFα-induced U937 cells	ERK	↓ CXCL-10	[67]
Panax notoginseng Saponins	Apolipoprotein-E deficient mice	-	↓ IL-6, TNF-α, VCAM, ICAM	[7]
Panax notoginseng Saponins	Zymosan A-induced mice	NF-κB	↓ MMP-2, MMP-9, IL-18, IL-1β, integrins	[6]
Panax notoginseng Saponins	Carbon tetrachloride-induced mice	-	↓ TGF-β, TNF-α, IL-6 ↑ IL-10	[43]
Panax notoginseng n-butanol extract	Collagen-induced arthritis mice	p38MAPK, JNK, ERK and NF-κB	↓ TNF-α, IL-1β, iNOS, MMP-13	[5]
Panax notoginseng ethanol extract	LPS, CpG or poly(I:C)-induced DC2.4 murine dendritic cells	-	↓ IL-6, TNF-α, CD40	[44]
Panax quinquefolius ethanol extract	LPS-induced RAW murine macrophages	STAT	↓ iNOS	[45]
Panax quinquefolius ethanol extract	Experimental colitis mice	-	↓ iNOS, COX-2, p53	[46]
Rb_1	TNF-induced endothelial cells	MAPK and NF-κB	↓ TNF-α	[47]
Rb_1	Capsaicin-induced HaCaT human keratinocyte	NF-κB	↓ IL-8, PGE2	[48]
Rb_1	IFN-γ, LPS/IL-1β–induced CIA mice	-	↓ TNF-α in PBMC, fibroblast-like synoviocytes and chondrocytes	[49]
Rd	Transient focal cerebral ischemia	-	↓ iNOS, COX-2	[50]
Rg_1	LPS-injected mice	p38MAPK, JNK and NF-κB	↓ TNF-α, iNOS and ionized calcium binding adaptor molecule-1	[51]

Table 1. *Cont.*

Rg_1	LPS-N9 microglial cells	NF-κB	↓ TNF-α, nitric oxide	[52]
Rg_1	CD4(+) T cells of Candida albicans-infected mice	-	↑ IL-2, IFN-γ	[53]
Rg_3	TPA-induced mouse skin cells and U937 promyelocytic leukemia cells	AP-1, NF-κB	↓ COX-2	[54]
Rg_3	Beta-amyloid-induced BV2 murine microglial cells	-	↓ TNF-α, IL-1β, IL-6, MCP-1, MIP-1γ	[55]
Rg_3	TNF-α-induced-ECV304 human endothelial cells	AKT	↓ VCAM-1, ICAM-1	[56,57]
Rh_1	IFN-γ-BV2 murine microglial cells	ERK, STAT1, IRF-1 and NF-κB	↓ Nitric oxide, reactive oxygen species, TNF-α	[58]
Rh_1	LPS-stimulated microglia	cAMP-dependent protein kinase	↑ IL-10, hemeoxygenase-1	[59]
Rh1	LPS-stimulated microglia	ERK and NF-κB	↓ iNOS, COX-2	[59]
Rh_1	Oxazolone-induced atopic dermatitis skin lesion in mice	-	↓ IL-6, IgE in peripheral blood ↑ Foxp3	[60]
Rh_1	LPS-induced RAW murine macrophages	NF-κB	↓ iNOS, COX-2	[61,62]
Rh_2	TNF-α-induced human astroglial cells	JNK and NF-κB	-	[63]
Rh_2	LPS/IFN-γ-induced BV2 microglial cells	AP-1	↓ Nitric oxide, COX-2, TNF-α, IL-1β	[64]
Rh_2	Rh2-induced BV2 murine microglial cells	-	↓ IL-10	[64]
Rh_2 & Rh_3	LPS-induced microglial cells	-	↓ iNOS, MMP-9, IL-1β,TNF-α	[65]
Rp_1	LPS-induced RAW murine macrophages	NF-κB	↓ IL-1β	[66]

AP-1: activator protein 1; COX: cyclooxygenase; ERK: extracellular signal regulated kinase; ICAM: intercellular cell adhesion molecule; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinases; LPS: lipopolysaccharide; MAPK: mitogen activated protein kinases; MCP: monocyte chemoattractant protein; MHC: major histocompatibility complex; MIP: macrophage inflammatory protein; MMP: matrix metalloproteinase; NF-kB: nuclear factor-kappaB; PGE: prostaglandin; PBMC: peripheral blood mononuclear cells; STAT: Signal Transducers and Activators of Transcription protein; TGF: Transforming growth factor; TNF: tumor necrosis factor; TPA: 12-*O*-tetradecanoylphorbol-13-acetate; VCAM: vascular cell adhesion molecule; ↓ : downregulation of expression; ↑ : upregulation of expression.

5. Application of Ginseng and Ginsenoside to TNF-α Mediated Inflammatory Diseases

TNF-α is a pleiotropic cytokine and its biological functions are varied and complex. It interacts with an array of other cytokines to initiate a cascade of cellular activities downstream. TNF-α induces expressions of vascular adhesion molecules on the endothelial cells and chemokines on macrophages and neutrophils to enhance cell trafficking [68-72]. In addition, TNF-α stimulates phagocytic functions of monocytes and macrophages to clear invading pathogens or cell debris. Hence, TNF-α production in acute infection is mostly beneficial to the host. However, excess uncontrolled production of TNF-α can cause over-induction of cytokines and chemokines including IL-1, IL-6, IL-8, growth-regulated oncogene, CXCL-10 and CCL-5. Additionally, the release of glucocorticoids may enhance local inflammation and cause tissue damage [14,73]. Several autoimmune and inflammatory diseases including rheumatoid arthritis [72], septic shock [74], Crohn's disease, psoriasis [75], and inflammatory bowel disease [76,77] are associated with dysregulated TNF-α production. As TNF-α is a good therapeutic target for treating inflammatory diseases, the identification of TNF-α antagonists from medicinal herbs and natural products, for example ginseng, could definitely provide an alternative for the treatment of debilitating inflammatory diseases. However, it has to emphasize that the anti-inflammatory effects of ginseng and/or ginsenosides cannot be attributed to lowering TNF-α only but also their immunoregulatory properties on innate and adaptive immunity as mentioned earlier.

6. Conclusions

Ginseng contains a complex mixture of chemical constituents that have multiple and diverse physiological effects on the human body. The anti-atherosclerotic, anti-arthritic, anti-oxidative and anti-allergic effects of ginseng and the ginsenosides in *in vitro* and *in vivo* studies may due to the their anti-inflammatory activity. However, the detailed molecular mechanisms of the anti-inflammatory activities of ginseng extracts and ginsenosides remain to be investigated.

During the last few decades, bioactivity-guided approach have been widely applied for isolation or identification of the bioactive compounds from herbs [78]. This approach can be extended further to another level by combining the different bioassay and the rapidly developed liquid chromatography and tandem mass spectrometry, and liquid chromatography and nuclear magnetic resonance technologies to determine not only the native bioactive compounds in medicinal herbs but also their structural interactions to the targets at the molecular level [79].

Competing Interests

The authors declare that they have no competing interests.

Author's Contributions

DCWL and ASYL wrote the manuscript together and experimental works cited are designed by both. Both authors have read and approved the final manuscript.

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