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Review article

Adaptogenic effects of *Panax ginseng* on modulation of immune functions

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A B S T R A C T

Traditional medicinal practices have used natural products such as adaptogens to treat inflammatory, autoimmune, neurodegenerative, bacterial, and viral diseases since the early days of civilization. *Panax ginseng* Myer is a common herb used in East Asian countries for millennia, especially in Korea, China, and Japan. Numerous studies indicate that ginseng can modulate the immune system and thereby prevent diseases. Although the human immune system comprises many different types of cells, multiple studies suggest that each type of immune cell can be controlled or stimulated by ginseng or its derivatives. Provisional lists of ginseng's potential for use against viruses, bacteria, and other microorganisms suggest it may prove to be a valuable pharmaceutical resource, particularly if higher-quality evidence can be found. Here, we reviewed the role of ginseng as an immune-modulating agent in attempt to provide a valuable starting point for future studies on the herb and the human immune system.

1. Introduction

Adaptogens are a unique class of "nutraceuticals," an alternative term for biologically active, plant-derived substances that can stabilize homeostasis and normalize metabolic functions. Several plants exhibit adaptogenic activity due to their diverse chemical compounds. The term "adaptogen" was introduced by Nikolay Lazarev, a prominent Russian scientist in 1940, when he described *Schisandra chinensis* (Turcz.) Bail [1] although it has recently been used as a functional term by some health authorities. Scientific studies have demonstrated that adaptogens exhibit neuroprotective, immune-modulating, anxiolytic, anti-fatigue, and central nervous system–stimulating activities, and they may be able to optimize hormone production and help balance physiological stress responses [2].

Ginseng is a noted adaptogenic herbs that has been utilized as a herbal remedy in East Asian countries since its discovery in the mountains of Manchuria, China, more than 5,000 years ago [3]. A member of the Araliaceae family, ginseng comprises 8 to 13 species of the *Panax* genus, including *P. ginseng*, all of which are usually recognized as "Asian or Chinese ginseng." *P. notoginseng* is known as "Sanchi" and *P. quinquefolius* is commonly called "American ginseng" [4]. The genus name *Panax* is orginated from "panacea" meaning a cure for all diseases. This terminology is at least partially

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true for ginseng as it has exerted its effective roles in a wide range of pharmacological uses [5]. *P. ginseng* Meyer, and Korean Red Ginseng (KRG) in particular, have been associated with diverse effects such as improvement of immunity, memory, and blood circulation, fatigue relief, antioxidation, and mitigation of menopausal symptoms. It also reportedly protects against cancer; cardiac diseases; inflammatory conditions; bacterial, viral or other microbial diseases; and neurological disorders [6]. The active components in KRG include ginsenosides, phenolic compounds, alkaloids, peptides, polysaccharides, and polyacetylene. Consumption habits of ginseng vary from culture to culture. In South Korea, its roots are distributed in four varieties. China, South Korea, Canada, and the US are the major producers of ginseng, and the global market is worth over $2 billion (USD) [7].

Ginseng as a dietary supplement modulates the immune system comprises of a complex network of different cells and proteins that protects the body from infections and can be divided into innate and acquired aspects (Fig. 1). Innate immunity is a first-line of defense instrument that onset the battle against intruding pathogens within four hours of exposure to an infectious agent [8]. Adaptive or acquired immunity is a second-line defense response that occurs days to weeks after exposure to microbial antigens. This mechanism is characterized by specificity, immunological memory, and self/non-self-recognition. The immune system is fundamental to survival; without it, our bodies would be vulnerable to attack by myriad pathogens [9]. However, different diseases or conditions can weaken an immune system through two forms of immunodeficiency disorders. Primary immunodeficiency disorders can be caused by genetic mutations and are usually present at birth, while secondary disorders may result from chronic conditions such as diabetes and cancer. Malnutrition or prolonged use of immunosuppressants can also weaken the immune system [10]. Natural products can act as immune-stimulating agents, and a number of phytochemicals that can enhance immune function, such as flavonoids, terpenoids, lignans, polyphenolics, sulfides, and saponins, have been identified, and some potent and natural antioxidant compounds are considered promising treatments for chronic diseases [11]. Natural dietary supplements are comparatively safe and cost-effective compared with synthetic products, which are often linked to side effects such as anemia, nausea, vomiting, and hair loss [12]. Ginseng may have the capability to play a pivotal role as a dietary supplement that enhances immunity, and numerous *in vivo* and *in vitro* investigations have revealed the anticancer, antidiabetic antioxidant, or adaptogenic properties of ginseng. Ginsenoside-Rb1 from *P. ginseng*, for example, can inhibit the formulation of tumor necrosis factor-alpha (TNF-α) lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages [13]. The results of a 2006 research by Shepherd et al regarding the immunomodulatory effect of *P. notoginseng* extract in the case of cultured macrophages (RAW264.7 cells) suggested the inhibiting capability of the extract on LPS-induced TNF-α and interleukin (IL)-6 production in a pattern depending on concentration [14]. Ginsan, a polysaccharide extract of *P. ginseng*, has been exhibited multiple immunomodulatory effects, and can inhibit p38 MAP kinase and the nuclear factor-kappa B (NF-κB) pathway [15]. In addition, the anti-inflammatory effects of ginsenosides make them beneficial to treat the inflammatory diseases [16].

Thousands of studies enumerate the role of ginseng in different diseases, and recent reports emphasize its role as an immune-modulating agent. Numerous *in vitro*, *in vivo* and clinical studies have elicited a role for ginseng in fostering immune system homeostasis and promoting the counteractions to illness and microbial invasions. In 1969, Israel Brekhman, the first pharmacologist who mentioned the *P. ginseng* as an adaptogen based on its nonspecific and tonic effects [17]. Since then, *P. ginseng* has demonstrated substantial promise as an adaptogen that can enhance physical performance and stress-resistance and mitigate the effects of aging through immunomodulatory effects [18]. In this article, we describe the prospective adaptogenic effects of P. ginseng on immune system modulation.

2. Effect of ginseng on innate immunity

Innate immunity is the first line of defense in opposition to various pathogens and antigens. It is a nonspecific defense mechanism mediated by a diverse set of receptors that belong to families of various proteins such as pattern-recognition receptors that directly detect a pathogen-associated molecular pattern (PAMP). Other proteins such as complement receptors and Toll-like receptors detect the products of PAMP recognition [19]. Both physical impediments (e.g., skin and the mucous membranes), and chemical impediments (acid in stomach, phagocytes, natural killer cells, cytokines, inflammatory chemicals, and bacteriolytic lysozymes in tears and saliva) are involved in this immune system. The innate

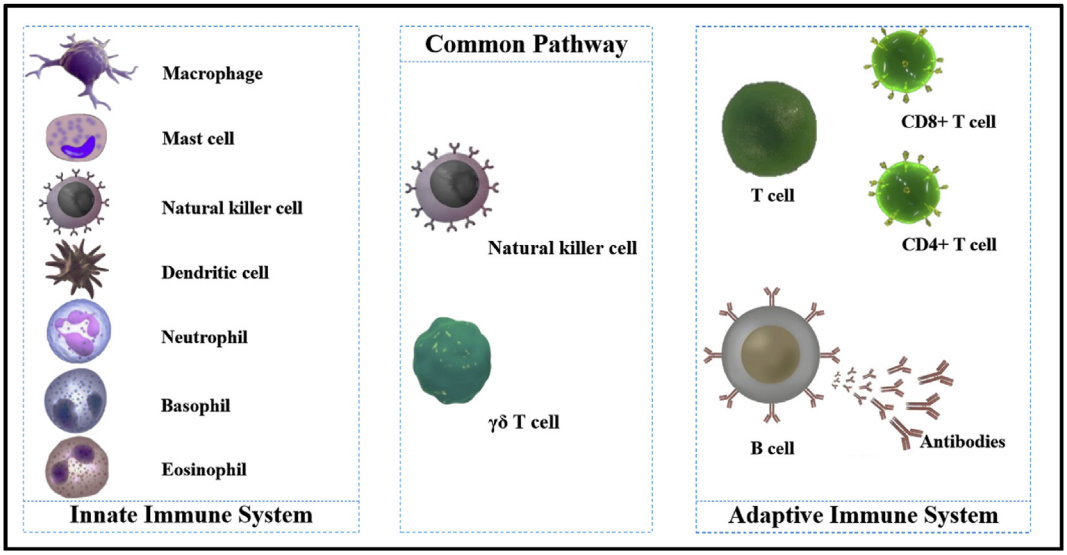

Fig. 1. Cells of the innate and adaptive immune system.

immune network becomes activated immediately or within a few hours of the appearance of an antigen. Unlike the adaptive immune system, which depends on T and B cells, the innate immune system is mediated by both myeloid cells (macrophages, dendritic cells, neutrophils, and eosinophils and lymphoid cells, such as natural killer cells [20]. Several investigations have reported that extract from ginseng or its components exhibit immunomodulation effects on innate immunity (Tables S1, S2, and S3). However, despite the different kinds of components linked to innate immunity, we kept our discussion limited to the consequences of ginseng on the components of cellular immune system.

2.1. Macrophages

Macrophages are immune cells that detect, engulf, and destroy pathogens and apoptotic cells via monocytic differentiation as they leave the blood. These cells are derived largely from yolk sac progenitors and myeloid cells that originate as hematopoietic stem cells in bone marrow [21]. These large phagocytic cells are found in all tissues, possess a substantial potential for autonomous self-renewal, and are considered important combatants in the innate defense system. Several investigations have claimed that ginseng extracts, ginsenosides, and the polysaccharides from it exhibit immunomodulating effects on macrophages. An aqueous extract from *P. ginseng* reportedly stimulated inducible nitric oxide, a reactive nitrogen species used against pathogens and synthesized in a dose-dependent manner in murine macrophages (RAW264.7 cells) [22]. Another study of the same cell line showed that wild ginseng extract upregulated the production of nitrate oxide (NO) cytokines, including IL-6, IL-1α, IL-1β, TNF-α, granulocyte-macrophage colony-stimulating factor, and the chemokines, e.g., macrophage chemotactic protein-1 [23]. The acidic fraction of polysaccharides from KRG reportedly increased phagocytic initiatives of the reticulo-endothelial system and antitumor effects against the solid formation of sarcoma-180 in Institute of Cancer Research (ICR) mice [24]. However, polysaccharides from ginseng can also trigger the fabrication of NO by activating inducible NO synthase (iNOS), and change cytokines level, such as IL-1, IL-6, and TNF-α [25]. Oligosaccharides co-cultured with RAW264.7 and B16F10 melanoma cells produced a similar result in a pattern depending of doses by activating the JNK, ERK, p38, and NF-κB pathways [26]. In addition, saponins or ginsenosides, signatory compounds of ginseng, enhanced phagocytic actions modulating macrophage activity. A ginsenoside derivative known as 20S-dihydroprotopanaxadiol upregulated macrophage phagocytic activity and increased sodium nitroprusside–derived radicals in RAW264.7 cells, and co-stimulatory expression of CD80 and CD86 in U937 cells [27]. Ginsenoside Rg3, *in vitro* and *in vivo* investigations, increased Fcγ receptor-mediated macrophage phagocytosis by enhancing the ERK1/2 and p38 MAPK pathways [28]. Another study found that ginsenosides Rg5 and Rk1 along with ginsenoside Rg3 elevated macrophage phagocytosis via ERK/c-Jun pathway, and raised NF-κB transcriptional activity, cytokine production (IL-6 and TNF-α), and MHC class I and II expression in RAW264.7 cells [29]. Again, ginsenoside Rg1 adjusted the macrophage responses by tuning the NF-κB and mTOR pathways. In that study, ginsenoside Rg1 augmented TNF-α, but diminished IL-6 in both LPS- activate mouse peritoneal macrophages and RAW 264.7 cells [30]. However, an *in vitro* investigation of cytokine using mouse macrophages found that Asian ginseng may not be capable to invigorating the immune functions. That study reported that, while the herb increased IL-12 expression at both the levels of mRNA and protein, it failed to change mRNA levels of IL-1 β, IL-15, MIP-1α or TNF-α, significantly [31].

2.2. Dendritic cells

Dendritic cells (DCs) derived from common myeloid stem-cell progenitors process antigen materials to present antigenic peptides to T cells in the messenger-like activity that resembles elements to both innate as well as adaptive immune responses among the mammals. After activation, DCs move to the lymph nodes, where they can communicate with naïve T lymphocytes to trigger more tailored immune responses against pathogens. They also make the T cells tolerizeable to antigens that innate to the body and thereby minimize autoimmune responses. Red ginseng extract (RGE) in an *in vitro* study enhanced the activity of surface co-stimulatory molecules, including CD80, CD40, and CD86, and major histocompatibility complex (MHC) class II, on DCs (BMDCs) originated from bone marrow, promoted the proliferation of allogeneic T cells, syngeneic CD4+ T cells and CD8+ T cells, and increased the IL-2 and IFN-γ generation [32].

Polysaccharides from ginseng also tend to show homogenous outcomes in *in vitro* studies. Ginsan-, glucopyranoside-, and fructofuranoside-containing polysaccharides enhance BMDC maturation, upregulating the production of markers such as CD86 and MHC class II, and the IL-12 and TNF-α fabrication [33]. Similarly, acidic polysaccharides (>99% purity) elevate the proliferation of BMDCs proliferation at 200 μg/mL, morphologically promote differentiation to DCs, and reduce phagocytosis by promoting differentiation. They also increase the expression of CD40, CD86, CD83, CD80, IL-12p70, TNF-α, and MHC class II [34]. Ginsenosides, the principal effective components of ginseng, also have immunomodulatory consequences on DCs. In an *in vitro* study in which CD14+ monocytes cleansed from peripheral blood mononuclear cells (PBMCs) of adult human treated with saponin from ginseng roots enhanced the TNF-α, IL-6, IL-10 fabrication, and inhibited both the production of TNF- α in LPS- sensitized monocytes and ERK1/2 as well as JNK activity, although it had no effect on IL-1 levels [35]. Saponins also reportedly reduce DC maturation markers, and the treatment of human PBMCs with saponin followed by oxidized low-density lipoprotein can reduce the release of cytokines such as TNF-α and IL-12, as well as the maturation markers CD40, CD86, CD1a, and HLA-DR [34]. In another *in vitro* study, flower leaf–derived floralginsenoside Kc, floralginsenoside J, and ginsenoside I showed suppressive consequences on the production of LPS-actuated IL-12, and floralginsenoside Kc also downregulated the production LPS-enliven IL-6 and TNF-α [36]. In addition, ginsenosides Rg6 and F4 obtained from flowers and leaves of steamed ginseng downregulated the production of IL-12 p20 in dendritic cells sourced from bone marrow [37].

2.3. Natural killer cells

Natural killer (NK) cells are key combatants in the innate immune system and a type of lymphocyte in circulation that can identify cells that are neoplastic and infected with virus as like non-self-elements through their recognition of MHC class I self-antigens [38]. NK cells constitute 5–20% of circulating lymphocytes in cells derived from bone marrow, as well as secondary lymphoid tissues from the spleen, tonsils, and the lymph nodes. Subsets of these cells express the upregulating Fc receptor, CD16, and most express CD56 in humans. Although NK cells resemble cytolytic functions of CD8+ cytotoxic T lymphocytes; but in contrary, these cells are “naturally” cytotoxic, and do not need previous antigen exposure to induce anti-tumor effects [39]. However, the oral administration of KRG for two months stimulated NK cells activity and improved the lipid profiles and impeded the steatohepatitis disease in Otsuka Long-Evans Tokushima Fatty rats [40]. Daily dietary intake of CVT-E002 (ginseng extract) for four weeks augmented the number of NK

cells in C3H juvenile (four-week-old) mice [41]. An *in vitro* study using PBMCs from normal individuals and patients having acquired immunodeficiency syndrome (AIDS) or chronic fatigue syndrome reported that the NK cell activity was ameliorated in normal, fatigued, and AIDS patients [42]. Several clinical studies have also claimed that aqueous extract obtained from ginseng can enhance NK cell activity. For example, a clinical trial involving 20 healthy individuals found that daily oral intake of 1,000 mg of a ginseng water extract for two weeks increased the cytotoxicity of NK cells [32].

3. Role of ginseng on adaptive immunity

Adaptive, or acquired, immunity is a defense system that provides a more tailored repository of remembrance for both self-antigens and extraneous antigens. This response system evolved from immunologic memory and involves strictly modulated communication among antigen-presenting cells and lymphocytes. The signature combatants of lymphocytes are B and T cells that are continuously produced from precursor stem cells located in the thymus and bone marrow. The B lymphocytes and the antibodies secreted from them collectively form the responses of humoral immune complex while T lymphocytes are portion of the responses derived from cell-mediated immune complex. These two cell types are usually produced concurrently, and responses often take place synergistically. The following section discusses the effects of ginseng and its compounds on both humoral as well as cell-mediated reactions of the acquired immune system (Tables S4 and S5).

3.1. Humoral immune response

The humoral immune response involves antibody-mediated activation of B cells and antibodies produced by plasma cells. This line of defense shields the host from invading pathogens through phagocytosis, neutralization of infectivity, or toxic effects, and by upregulating complementary activities [38]. Five classes of antibodies, including immunoglobin (Ig) A, IgD, IgE, IgG, and IgM, are derived from B cells. Alteration of the antibodies, or the organs from which they are produced, affects the humoral immune reactions and the interconnected defense system of the body. Several *in vitro* as well as *in vivo* studies and clinical trials have evaluated the effects of ginseng and its compounds on humoral immune responses. When ginseng radix from ginseng root extract was dispensed orally to male BALB/c mice for five consecutive days, serum IgG levels decreased while IgA levels increased and IgM levels remained same. In this dose-dependent study, IL-10 and T-helper 1 (Th1)-type cytokines (IL-2 and IFN-γ) secreted by regulatory T cells type 1 increased when Con A was stimulated in the spleen cells of mice treated with ginseng, but levels of IL-4 (Th2-type cytokine) were unchanged, and the activity of NK cell and the CD4+/CD3, CD8+/CD3 cells were reduced in the ginseng group [43]. When the extract was administered in the same way in the same type of mice for 30 consecutive days, spleen cells decreased IgG and IgA production, but mice medicated with ginseng and OVA immunization showed no effect on IgG production in spleen cells. Besides, the secretion of IL-2, IL-4, and IFN-γ was suppressed whereas the production of IL-10 remained the same in both ovalbumin-immunized and ginseng-medicated mice compared with a control group [43]. In the case of intraperitoneal injection for three consecutive days, an ethanol extract with a concentration of 50% obtained from ginseng upregulated IgM, IgG, and IgA, but reduced IgA at high doses in mice spleens by enhancing synthesis of Th1-type (IL-2 and IFN-γ) as well as Th2-type (IL-4, IL-10) cytokine [44]. The signature compounds of this herb, ginsenosides, can affect B-cell proliferation and antibody production. In a mouse model study, the ginsenosides Rg1 and Rg3 increased IgA production compared with LPS alone but had no effect on IgM, IgG1, and IgG2b, with B cells differentiating into cells producing IgA through germline transcript-α expression [45].

3.2. Cell-mediated immune response

Naïve T lymphocytes trigger the cell-mediated immune response to fabricate effector T cells after encountering antigens specific for that particular T cell. The cells that present antigens to the innate immune complex communicate with helper T cells to roll out this response, which detects and annihilates viruses, bacteria, and cancer cells. Although the protective mechanism is not characterized primarily by antibodies, it has a vital role in antibody synthesis and delayed-type hypersensitivity [46]. However, studies have found that ginseng and its compounds exhibit modulatory effects on the cell-mediated immune response. KRG reportedly induced immunosuppressive regulation in mice by promoting IFN-γ + CD4 + T cells, IFN-γ T-cell (reg) production, but did not influence the production of IL-4, IL-4+, and CD4+ cells [47]. Ginseng extract can also stimulate a cellular immune response by enhancing antibody production according to cytotoxicity. Ginseng root water extract administered to mice for six days increased IgM and IgG production capacity against sheep red blood cells [48]. Ginsenosides isolated from KRG can increase the secretion of T-cell growth factor regulator IL-2 in phorbol 12-myristate 13-acetate (PMA)/ionomycin (Io)-actuated EL-4 T cells in a dose-dependent manner [49]. Dammarane triterpene 27-demethyl-(E,E)-20(22),23-dien-3β,6α,12β-trihydroxydammar-25 -one extracted from *P. ginseng* leaves had a similar effect in case of cellular immune reactions *in vitro*, and decreased the expression of IL-4 as well as IL-6 at 100 ng/mL on ConA-enliven splenocytes [50]. Ginsenosides Rc as well as Rd also stimulated the cellular immune reactions by promoting T-cell proliferation along with slightly increasing NK cell activity. These two saponins also suppressed the multidrug resistance efflux pump [51]. Ginsenoside Rg1 increased CD+4 T-cell proliferation and also the expression of IL-4 mRNA in an *in vitro* study, but diminished IFN-γ mRNA expression. Besides, this saponin induced the conversion of a Th1 pattern to a Th2 pattern immune response [52]. Oligopeptides from ginseng administered intragastrically to mice for 30 days also stimulated the augmentation of Th as well as T cells, secretion of IL-2, IL-12, and IL-6, and the production of IgG1, IgG2b, and IgA [53]. However, multiple studies confirm that *P. ginseng* exhibits immunomodulating consequences on innate as well as adaptive immunity, indicating adaptogenic behavior.

4. Antibacterial effects of ginseng

Antibiotics are primarily used to treat and prevent bacterial infections. Unfortunately, antibiotic resistance is spreading in different parts of the world and has become a major public health threat. Antibiotic resistance can occur naturally, but overuse of antibiotics is accelerating the process. A novel antimicrobial agent, especially from a herbal source, may present opportunities to address this problem, and numerous studies (Tables S6) have revealed that ginseng extract or its components possess bactericidal properties. *Helicobacter pylori* is a Gram-negative bacterium that infects 50% of the world's population. KRG extract has exhibited a protective effect against this bacteria by reducing cytotoxicity and DNA mutagenesis induced by *H. pylori*, and can reduce proinflammatory activity in gastric mucosal cells [54]. *Bacillus cereus* is a Gram-positive, spore-forming, facultative anaerobe bacterium that expresses several virulence factors as emetic toxins and enterotoxins. Ginseng treatment reportedly has a beneficial

effect against *B. cereus* [55]. Na et al demonstrated that extract yields in the form of ginsenosides exhibit impeding consequences against *B. cereus* and *Staphylococcus aureus*, with methanol extracts obtained from heated ginseng showing more antimicrobial activity than the ethanol extracts [56]. *Pseudomonas aeruginosa* is a rod-shaped, Gram-negative bacterium that causes infections in the lungs (pneumonia), the blood, and other parts of the body after surgery. This bacterium uses a cell-to-cell communication network recognized as quorum sensing during the infectious process and N-acylated homoserine lactone as a signal molecule. Another study revealed that ginseng treatment permitted animals transmitted with *P. aeruginosa* pneumonia to successfully remove bacterial infections [57]. Another study suggested that ginseng application can help to exterminate biofilm-linked chronic infections caused by *P. aeruginosa* [58]. A gram-positive bacterium named *S. aureus* that colonizes the skin, respiratory tract, and bloodstream, can trigger different clinical infections. Ginsan, a polysaccharide from *P. ginseng* that induces NO production and shows promising phagocytic activity, can stimulate macrophages to enhance anti-septicemic activity. Ginsan treatment can also increase proinflammatory cytokine production in the murine fibroblast cell line L929 [59]. Sung et al reported that a combination of KRG saponins with kanamycin and cefotaxime produced a synergistic action against methicillin-resistant *S. aureus* [60]. *Listeria monocytogenes* is a small, rod-shaped, Gram-positive, facultatively anaerobic bacterium that induces listeriosis (). One study suggested that all ginseng extracts inhibit the growth of *B. cereus*, *Salmonella enteritidis*, *Escherichia coli,* and *L. monocytogenes*. However, among the bacteria, *B. cereuses* was the most sensitive to ginseng extract by subcritical water extraction at 190°C, suffering disrupted cell membranes [61]. *Streptococcus pneumoniae* (pneumococcus) is a Gram-positive bacterium that can induce community-acquired pneumonia. A study of pneumococcal sepsis showed that mice pre-treated with KRG (100 mg/kg) had significantly higher survival rates and body weights compared with non-treated controls. KRG pre-treatment also subdued Toll-like receptor (TLR) 4 and TNF-α expression in RAW 264.7 macrophage cells and enhanced cell survival using the signaling pathway of phosphoinositide 3-kinase (PI3K)/AKT [62]. *Porphyromonas gingivalis* is a Gram-negative, rod-shaped bacterium that causes periodontal diseases and colonizes the gastrointestinal and respiratory tracts and the colon. One study revealed that heat-transformed saponins can easily disrupt cell integrity and display potential antibacterial activity against *P. gingivalis* [63].

5. Anti-viral effect of ginseng

Viruses are submicroscopic infectious parasites that can replicate only in living cells of animals, plants, fungi, or bacteria. They are composed of genetic material (DNA or RNA) enclosed in a protein coat and can cause organ-specific infectious diseases such as the common cold, influenza, diarrhea, and hepatitis, as well as autoimmune diseases, cancer, and immunodeficiency. Recent and rapid epidemics of viral diseases around the world pose serious threats to public health. As a result, new resources are being directed to the development of vaccines to prevent infection, antiviral drugs to treat infection, and diagnostic products. However, many vaccines that control viruses have yet to be approved, and few viruses can be controlled by antiviral drugs. Herbal medicines are considered novel antiviral alternatives [64]. Ginseng extract may be an effective modulator for both natural and acquired immunity regarding viral infection. Influenza virus is the most common human respiratory pathogen, causing both seasonal, endemic infections and periodic, unpredictable pandemics. Several *in vitro* and *in vivo* studies have demonstrated the antiviral effects of ginseng on influenza infection (Tables S7). Kang et al from Georgia State University reported that KRG extract treatment can improve the viability of human alveolar epithelial A549 cells upon H1N1 infection and decrease virus-induced cytokine secretion and reactive oxygen species formation [65]. Park et al used mouse and ferret models to support the use of ginseng as a dietary tool to enhance immunity against the H5N1 influenza virus through interferon (IFN)-alpha and -gamma (IFN-α and IFN-γ) [66]. Moreover, KRG extracts also act as mucosal adjuvants against influenza virus A/PR8 during viral infection [67]. Human immunodeficiency virus (HIV) destroys and impairs the function of immune cells. An HIV-positive patient is diagnosed with AIDS when CD4+ cell counts fall < 200 cells/mm^3. Negative factor (nef) is a virulence factor that secures T-cell activation and the establishment of a persistent state of infection early in the HIV life cycle. A few studies have reported that KRG can increase the frequency of gross deletion in the nef gene, and as a result it can delay the progression in HIV-1 patients (Table S7). Other clinical studies have revealed a role for KRG in HIV patients (Table S7). For an example, Young-Keol Cho and his team reported that KRG intake of 4,082 $\pm$ 3,928 g over 111.9 $\pm$ 31.3 months can decrease CD4 T-cell counts, significantly slowing the depletion of CD4 T cells irrespective of HLA class I [68]. Cho et al.'s study of 252 patients with a diagnosis of HIV-1 between 1986 and 2013 analyzed survival duration of those who did and did not consume KRG. In 162 patients treated with 3,947 $\pm$ 4,943 g of KRG for 86 $\pm$ 63 months, a significant correlation was seen between KRG amount and survival duration. Annual CD4+ T-cell counts decreased significantly more slowly in the KRG treatment group compared with the control group (48 $\pm$ 40 change in cells/μL vs. 106 $\pm$ 162 change in cells/μL; $p < 0.001$, respectively). Moreover, survival duration was significantly longer in the KRG group compared with the non-KRG group (101 $\pm$ 64 months vs. 59 $\pm$ 40 months; $p < 0.01$, respectively) [68]. It has been reported that ginsenosides Rh1 and Rb1 and compound K can inhibit the cytoprotective effects that lead to long-term survival [69]. Hepatitis B virus (HBV) is a double-stranded DNA virus that infects over 300 million individuals per annum globally and is a common reason for liver disease as well as liver cancer. Ginsenoside Rg3 can significantly inhibit the secretion of HBsAg, HBeAg, and viral particles in HBV-infected HepG2.2.15 cells [70]. Respiratory syncytial virus (RSV) is a negative single-stranded RNA virus in the Paramyxoviridae family. It is a major cause of severe respiratory disease and lung inflammation (pneumonia) in infants. KRG extracts reportedly protected human epithelial cells from RSV-induced cell death and viral replication, and an RSV-infected mice model showed that the treatment with RGE ameliorated viral clearance from lungs, improved IFN-γ synthesis production, and increased CD8+ T cells and CD11c + DCs [71]. Ginsenosides Re, Rf, and Rg2 showed significant antiviral activities against rhinovirus and coxsachievirus, Rg2 showed anti-enterovirus activity. Moreover, KRG, and ginsenosides Rb1 and Rg1 reduced feline calicivirus and murine norovirus titer (Table S7).

6. Antifungal effects of ginseng

Skin, nail, and hair are usually infected with fungi, over 150 million people around the world experiencing serious cases, and this infection can be fatal [72]. Most of the fungal infections are caused by yeasts or dermatophytes, such as *Epidermophyton*, *Microsporum*, and *Trichophyton*. However, the opportunistic fungal organism *Candida albicans* can cause disease during immunosuppressive conditions. Multiple investigations have described the consequences of ginseng or ginseng derivatives usage in case of fungal infections. For example, a study by Linda A. Toth on *C. albicans* infection found that ginseng extract did not significantly change overall morbidity or mortality, but significantly reduced

concentrations of some inflammatory cytokines in the kidney and/or serum [73]. Another study, conducted by Sung and Lee, showed that 100 mg/mL doses of ginsenosides had positive impacts on *C. albicans* infection, compared with a positive control of amphotericin B at a concentration of 2.5 mg/mL [74]. Sung et al described the fungicidal effect of ginseng, with ginsenosides showing antifungal activity by disrupting cell membranes [74]. *P. ginseng* and its various constituents showed significant pharmacological and therapeutic effects against viruses, bacteria or other microorganisms, indicating its potential adaptogenic behavior.

7. Anticancer effect of ginseng

Medicinal herbs and the phytocompounds originated from them are considered as beneficial complementary treatments for cancer, the leading cause of death around the globe. Studies have revealed that ginseng and its extracts, such as compound K and ginsenosides Rh1, F2, Rg3, and Rp1, have anticancer properties (Table S8). KRG can reportedly repress the viability of RMA cells in a dose-dependent pattern and can suppress inflammatory cytokines factors such as IL-4 and IL-5 [75]. Liu et al reported that the ginsenoside 20(R)-Rg3 can significantly inhibit cancer continuance in ovarian cancer cells by diminishing the expression of hypoxia-inducible factor-1α [76]. In addition, ginsenoside Rd can down-regulate expression of iNOS, COX-2, and NF-κB and suppress the phosphorylation of extracellular signal-regulated kinase and, in liver cancer, ginsenosides Rd and Rh2 can inhibit tumor migration and metastasis [77]. Boo et al, who evaluated the effect of KRG extract on immune modulation in a clinical setting, measured circulating IL-2, IL-8, and IL-10 as immune modulators in curative-surgery patients with advanced colon cancer. Their results showed that ginseng extract had an immunomodulatory effect in all three cases [78]. In addition, the study showed that ginsenosides Rg3, Rg5, and Rk1 can significantly suppress human prostate cancer cells both in case of *in vitro* and *in vivo* by provoking apoptotic cell death and autophagy [66]. Ginseng administered long-term may decrease the incidence of cancer [64], as suggested in a report by Yun et al on stomach and lung cancers [79]. Despite these encouraging reports, more research is required to evaluate the mechanism responsible for ginseng's anti-cancer affects.

8. Effect of ginseng on autoimmune disease

Autoimmunity refers to the deregulated process of immune-response pathogens and others factors that stimulate chronic inflammatory responses upregulating Th1 and Th17, TNF-α and the generation of IL-17, IL-22, IFN-γ, and IL-21, which initiate inflammation, producing antibodies, and leading to tissue injury [79]. However, in case of multiple sclerosis and other diseases related to chronic inflammation, oral- or vehicle-administered aqueous extract of North American ginseng decreased the clinical symptom of autoimmune encephalomyelitis, circulating TNF-α levels, iNOS levels in the central nervous system, and demyelination scores in C57BL/6J mice immunized with the MOG(35−55) peptide [80]. In mice with autoimmune encephalomyelitis (EAE), KRG and ginsenosides Rb1 and Rg1 ameliorated the condition by impeding Th1 and Th17 cells and activating regulatory T cells in mice [81]. KRG extract alleviated rheumatoid arthritis in mice with collagen-induced arthritis by regulating Th17 and promoting T-reg cells reciprocally by suppressing STAT3 phosphorylation [82]. Ginsenosides Rb1, Rh1, Rg1, and Rg3 downregulated the humoral immunity related to systemic lupus erythematosus blocking B-cell secretion and proliferation. Highly pruritic chronic inflammatory disease named atopic dermatitis (AD), elevates serum IgE levels, and markedly increases levels of inflammatory cells [83]. The equipoise of Th1 and Th2 is crucial regarding the pathogenesis of AD from an immunological perspective, and controlling the delicate equilibrium among Th1, Th2, and Th17/22 and T-reg cells is crucial to the control of AD. Cho et al suggested KRG can serve preventive as well as therapeutic functions through modulating the immune network at the early stages of AD. Oral KRG has been shown to obstruct the progression of the cutaneous inflammation in an AD animal model by hindering the DCs, thymic stromal lymphopoietin, and Th2 cytokines [83].

9. Ginseng as an adjuvant

Adjuvants refer to agents or components with little or no antigenic effects or characteristics beyond enhancing the immunogenicity of a medication or vaccine blended with it. It can also decrease the dose needed to achieve protection [84]. Contemporary studies have reported that adjuvants can upregulate or mature antigen-presenting cells, improve their antigen-uptake capacity, set off the synthesis of cytokines, turn on the inflammasomes, enhance the biological half-life of vaccines, and promote local inflammation and cellular recruitment. However, the selection of adjuvant depends upon the parity of its efficacy and the side-effects. Oral administration of KRG extract mixed with anionic macromolecules extracted from codium fragile activated the expression of COX-2, iNOS, and TLR-4, as well as IL-1β, IL-6, TNF-α, and IFN-γ in peritoneal macrophage cells of immune-suppressed mice at greater rates than observed with a ginseng-treated group [85]. With vitamin C, KRG upregulated NK and T cells, and suppressed the lytic cycle of virus, decreasing lung inflammation due to H1N1 infection [86]. As an adjuvant, Berry extract of ginseng promoted bone marrow−derived DCs and Th1 and Tc1 cells, and upregulated CD86, MHC class I and II, and the synthesis of IL-6, IL-12, and TNF-α in spleen DCs [87]. However, saponins of ginseng (ginsenosides) also exhibit immunomodulatory effects as an adjuvant. As a vaccine adjuvant, orally applied ginseng leaf-stem saponins (GSLS) with live infectious bursal disease vaccine in chicken enhanced both humoral and gut mucosal immune responses [88]. With selenium, the GLSL provoked IgB-specific serum antibody responses (IgG, IgG1, and IgG2a) and promoted lymphocyte proliferation and cytolytic activity of NK cells, along with the production of cytokines (IFN-γ, IL-12, IL-5, and IL-10) by splenocytes in mice against pseudorabies virus [89]. In case of foot-and-mouth disease, GLSL as a vaccine supplement with a mixture of an oil-induced higher IgG titer, and IFN-γ (Th1 cytokine) and IL-5 (Th2 cytokine) levels produced by splenocytes that were subcutaneously injected into immunized mice [90]. The orally administered GLSL increased IgA + cells and intestinal intraepithelial lymphocytes in chickens were vaccinated with live Newcastle disease [91]. The ginsenoside Rg1 stimulated humoral and cellular responses against *Toxoplasmosis gondii* in ICR mice subcutaneously immunized with *T. gondii* recombinant surface antigen 1 [92]. As a vaccine adjuvant, ginsenoside Rg1 triggered IgG, splenocyte proliferation, and mRNA expression of cytokines IL-4, IL-10, IL-12, and IFN-γ, and transcription factors GATA-3 and T-bet by splenocytes in C3H/HeB mice [93]. In BALB/c mice, ginsenoside Rg1 as an adjuvant to subcutaneous immunization increased both Th1 (IgG1 and IL-5) and Th2 (IgG2a, IFN-γ, and DTH) responses [94]. Ginsenoside Rd also showed similar adjuvant activities in ovalbumin-immunized mice by controlling the fabrication and the gene expression related to Th1 and Th2 cytokines [95]. In ICR mice subcutaneously immunized with inactivated H3N2 influenza virus antigen, ginsenoside Re increased serum-specific IgG, IgG1, IgG2a, and IgG2b responses, IFN-γ and IL-5 secretions, and lymphocytes [96]. For a DC−based vaccine, one study showed that M4 can be used as an adjuvant in immunotherapy [97]. The ginsenosides Rg1, Re, Rg2, Rg3, and Rb1

enhanced splenocyte proliferative responses and the production of both IL-5 and IFN-γ in mice subcutaneously immunized with ovalbumin [98]. Ovalbumin co-administered with ginsomes (ginsenoside Rb1, Rb2, Rc, and Rd–based nanoparticles) enhanced the levels of IgG1, IgG2a, IgG2b, and IgG3, and T- and B-lymphocyte proliferation in ICR mice [99]. Polysaccharides from ginseng also enhanced humoral and cellular immune reactions by increasing ovalbumin-specific Th1 (IL-2, IFN-γ, and GM-CSF), and Th2 (IL-10) cytokines [100].

10. Conclusion

Ginseng has opened new avenues in boosting immunity and treating immunity-related disorders. Among all herbal supplements, ginseng is the most widely studied, demonstrating promising beneficial effects with lower toxic effects and potential adaptogenic effects on the immune system. However, most immunomodulatory studies are limited to *in vitro* or animal models, and few have examined the impact of ginseng in clinical settings. Ginseng has been shown to enhance host immunity both actively and passively, and possible uses as a vaccine adjuvant against different infections, autoimmune conditions, and bacterial or viral diseases, have been proposed. This review describes the potential roles of ginseng in immunomodulatory therapy and provides a foundation for further research of the potential role of *P. ginseng* in treating immunity and immunodeficiency disorders. Ginseng appears to be a promising immunomodulatory agent, and resources should be devoted to studying the impact of ginseng on the human immune system.

11. Future perspectives

This review epitomizes the available data about the adaptogenic promises of *P. ginseng* with respect to the immune system. It is a need to evaluate mechanistic approaches to confirm the role of *P. ginseng*'s adaptogenic properties on the human immune system. Future clinical and pre-clinical studies should evaluate the immunomodulatory effects of ginseng.

Author contributions

Conceptualization, Z.A.R., S.H.Y., H.H., H.S.H., and J.Y.C.; writing—original draft preparation, Z.A.R and, S.H.Y.; writing—review and editing, H.H., H.S.H., and J.Y.C.; visualization, M.F.H. and J.K.K.; supervision, J.Y.C.; project administration, Y.S.K. and C.K.H..; funding acquisition, J.Y.C. All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

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References

[1] Tabachnik B. Adaptogens—natural protectors of the immune system, potentiating health and the crisis of the immune system. Springer; 1997. p. 143–7.
[2] Panossian A. Understanding adaptogenic activity: specificity of the pharmacological action of adaptogens and other phytochemicals. Ann N Y Acad Sci 2017;1401:49–64.
[3] Nair R, Sellaturay S, Sriprasad S. The history of ginseng in the management of erectile dysfunction in ancient China (3500-2600 BCE). Indian J Urol 2012;28:15–20.
[4] Yun TK. Brief introduction of *Panax ginseng* CA Meyer. J Kor Med Sci 2001;16: S3.
[5] Buettner C, Yeh GY, Phillips RS, Mittleman MA, Kaptchuk TJ. Systematic review of the effects of ginseng on cardiovascular risk factors. Ann Pharmacother 2006;40:83–95.
[6] Ratan ZA, Haidere MF, Hong YH, Park SH, Lee J-O, Lee J, Cho JY. Pharmacological potential of ginseng and its major component ginsenosides. J Ginseng Res 2020. https://doi.org/10.1016/j.jgr.2020.02.004. In press.
[7] Baeg I-H, So S-H. The world ginseng market and the ginseng (Korea). J Ginseng Res 2013;37:1–7.
[8] Beutler BJM. Innate immunity: an overview 2004;40:845–59.
[9] Roberts NA. The Immune system. Yale J Biol Med 2015;88. 99-99.
[10] Chapel H, Prevot J, Gaspar HB, Español T, Bonilla FA, Solis L, Drabwell J. Editorial board for working party on principles of care at I. Primary immune deficiencies - principles of care. Front Immunol 2014;5. 627-627.
[11] Khodadadi S. Role of herbal medicine in boosting immune system. Immunopathol Persa 2015;1:e01.
[12] Lee JH, Min DS, Lee CW, Song KH, Kim YS, Kim HP. Ginsenosides from Korean Red Ginseng ameliorate lung inflammatory responses: inhibition of the MAPKs/NF-κB/c-Fos pathways. J Ginseng Res 2018;42:476–84.
[13] Kim JH, Yi Y-S, Kim M-Y, Cho JY. Role of ginsenosides, the main active components of *Panax ginseng*, in inflammatory responses and diseases. J Ginseng Res 2017;41:435–43.
[14] Rhule A, Navarro S, Smith JR, Shepherd DM. *Panax notoginseng* attenuates LPS-induced pro-inflammatory mediators in RAW264.7 cells. J Ethnopharmacol 2006;106:121–8.
[15] Friedl R, Moeslinger T, Kopp B, Spieckermann PG. Stimulation of nitric oxide synthesis by the aqueous extract of *Panax ginseng* root in RAW 264.7 cells. Br J Pharmacol 2001;134:1663–70.
[16] Zhou Y, Yang Z, Gao L, Liu W, Liu R, Zhao J, You J. Changes in element accumulation, phenolic metabolism, and antioxidative enzyme activities in the red-skin roots of *Panax ginseng*. J Ginseng Res 2017;41:307–15.
[17] Brekhman II, Dardymov IV. New substances of plant origin which increase nonspecific resistance. Annu Rev Pharmacol 1969;9:419–30.
[18] Kim J-H. Pharmacological and medical applications of *Panax ginseng* and ginsenosides: a review for use in cardiovascular diseases. J Ginseng Res 2018;42:264–9.
[19] Medzhitov R, Janeway Jr CA. Innate immunity: the virtues of a nonclonal system of recognition. Cell 1997;91:295–8.
[20] Medzhitov R, Janeway Jr C. Innate immunity. N Engl J Med 2000;343:338–44.
[21] Perdiguero EG, Geissmann F. The development and maintenance of resident macrophages. Nat Immunol 2016;17:2–8.
[22] Jang HI, Shin HM. Wild *Panax ginseng* (*Panax ginseng* C.A. Meyer) protects against methotrexate-induced cell regression by enhancing the immune response in RAW 264.7 macrophages. Am J Chin Med 2010;38:949–60.
[23] Kang S, Min H. Ginseng, the 'Immunity Boost': the effects of *Panax ginseng* on immune system. J Ginseng Res 2012;36:354–68.
[24] Wang J, Zuo G, Li J, Guan T, Li C, Jiang R, Xie B, Lin X, Li F, Wang Y, et al. Induction of tumoricidal activity in mouse peritoneal macrophages by ginseng polysaccharide. Int J Biol Macromol 2010;46:389–95.
[25] Shin J-Y, Song J-Y, Yun Y-S, Yang H-O, Rhee D-K, Pyo S. Immunomodulating effects of acidic polysaccharides extract of *Panax ginseng* on macrophage function. Immunopharmacol Immunotoxicol 2002;24:469–82.
[26] Seo JY, Lee CW, Choi DJ, Lee J, Lee JY, Park YI. Ginseng marc-derived low-molecular weight oligosaccharide inhibits the growth of skin melanoma cells via activation of RAW264.7 cells. Int Immunopharmacol 2015;29:344–53.
[27] Kim MY, Cho JY. 20S-dihydroprotopanaxadiol, a ginsenoside derivative, boosts innate immune responses of monocytes and macrophages. J Ginseng Res 2013;37:293–9.
[28] Xin C, Quan H, Kim JM, Hur YH, Shin JY, Bae HB, Choi JI. Ginsenoside Rb1 increases macrophage phagocytosis through p38 mitogen-activated protein kinase/Akt pathway. J Ginseng Res 2019;43:394–401.
[29] Shin M-S, Song JH, Choi P, Lee JH, Kim S-Y, Shin K-S, Ham J, Kang KS. Stimulation of innate immune function by *Panax ginseng* after heat processing. J Agric Food Chem 2018;66:4652–9.
[30] Wang Y, Liu Y, Zhang X-Y, Xu L-H, Ouyang D-Y, Liu K-P, Pan H, He J, He X-H. Ginsenoside Rg1 regulates innate immune responses in macrophages through differentially modulating the NF-κB and PI3K/Akt/mTOR pathways. Int Immunopharmacol 2014;23:77–84.
[31] Wang H, Actor JK, Indrigo J, Olsen M, Dasgupta A. Asian and Siberian ginseng as a potential modulator of immune function: an *in vitro* cytokine study using mouse macrophages. Clin Chim Acta 2003;327:123–8.

[32] Kang S, Min H. Ginseng, the 'Immunity Boost': the effects of *Panax ginseng* on immune system. J Ginseng Res 2012;36:354–68.
[33] Lee J-H, Shim JS, Chung M-S, Lim S-T, Kim KH. Inhibition of pathogen adhesion to host cells by polysaccharides from *Panax ginseng*. Biosci Biotechnol Biochem 2009;73:209–12.
[34] Wang Z, Meng J, Xia Y, Meng Y, Du L, Zhang Z, Wang E, Shan F. Maturation of murine bone marrow dendritic cells induced by acidic Ginseng polysaccharides. Int J Biol Macromol 2013;53:93–100.
[35] Kim SH, Park JG, Sung GH, Yang S, Yang WS, Kim E, Kim JH, Ha VT, Kim HG, Yi YS, et al. Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain. Mol Nutr Food Res 2015;59:1400–5.
[36] Liu T-G, Huang Y, Cui D-D, Huang X-B, Mao S-H, Ji L-L, Song H-B, Yi C. Inhibitory effect of ginsenoside Rg3 combined with gemcitabine on angiogenesis and growth of lung cancer in mice. BMC Cancer 2009;9:250.
[37] Tung NH, Quang TH, Son JH, Koo JE, Hong HJ, Koh YS, Song GY, Kim YH. Inhibitory effect of ginsenosides from steamed ginseng-leaves and flowers on the LPS-stimulated IL-12 production in bone marrow-derived dendritic cells. Arch Pharm Res 2011;34:681–5.
[38] Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol 2015;16:343–53.
[39] Abel AM, Yang C, Thakar MS, Malarkannan S. Natural killer cells: development, maturation, and clinical utilization. Front Immunol 2018;9:1869.
[40] Hong SH, Suk KT, Choi SH, Lee JW, Sung HT, Kim CH, Kim EJ, Kim MJ, Han SH, Kim MY, et al. Anti-oxidant and natural killer cell activity of Korean red ginseng (*Panax ginseng*) and urushiol (*Rhus vernicifera* Stokes) on non-alcoholic fatty liver disease of rat. Food Chem Toxicol 2013;55:586–91.
[41] Miller SC, Ti L, Shan J. Dietary supplementation with an extract of North American ginseng in adult and juvenile mice increases natural killer cells. Immunol Invest 2012;41:157–70.
[42] See DM, Broumand N, Sahl L, Tilles JG. *In vitro* effects of echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. Immunopharmacology 1997;35:229–35.
[43] Liou CJ, Huang WC, Tseng J. Short-term oral administration of ginseng extract induces type-1 cytokine production. Immunopharmacol Immunotoxicol 2006;28:227–40.
[44] Sun X, Kong L, Zhou L. Protective effect of *Fructus corni* polysaccharide on hippocampal tissues and its relevant mechanism in epileptic rats induced by lithium chloride-pilocarpine. Exp Ther Med 2018;16:445–51.
[45] Park HY, Lee SH, Lee KS, Yoon HK, Yoo YC, Lee J, Choi JE, Kim PH, Park SR. Ginsenoside Rg1 and 20(S)-Rg3 induce IgA pProduction by mouse B cells. Immune Netw 2015;15:331–6.
[46] Wahren B, Morfeldt-Månsson L, Biberfeld G, Moberg L, Sönnerborg A, Ljungman P, Werner A, Kurth R, Gallo R, Bolognesi D. Characteristics of the specific cell-mediated immune response in human immunodeficiency virus infection. J Virol 1987;61:2017–23.
[47] Heo SB, Lim SW, Jhun JY, Cho ML, Chung BH, Yang CW. Immunological benefits by ginseng through reciprocal regulation of Th17 and Treg cells during cyclosporine-induced immunosuppression. J Ginseng Res 2016;40:18–27.
[48] Jie YH, Cammisuli S, Baggiolini M. Immunomodulatory effects of *Panax ginseng* C.A. Meyer in the mouse. Agents Actions 1984;15:386–91.
[49] Vinh LB, Park JU, Duy LX, Nguyet NTM, Yang SY, Kim YR, Kim YH. Ginsenosides from Korean red ginseng modulate T cell function via the regulation of NF-AT-mediated IL-2 production. Food Sci Biotechnol 2019;28:237–42.
[50] Tran TL, Kim YR, Yang JL, Oh DR, Dao TT, Oh WK. Dammarane triterpenes from the leaves of *Panax ginseng* enhance cellular immunity. Bioorg Med Chem 2014;22:499–504.
[51] Berek L, Szabó D, Petri IB, Shoyama Y, Lin YH, Molnár J. Effects of naturally occurring glucosides, solasodine glucosides, ginsenosides and parishin derivatives on multidrug resistance of lymphoma cells and leukocyte functions. In Vivo 2001;15:151–6.
[52] Lee EJ, Ko E, Lee J, Rho S, Ko S, Shin MK, Min BI, Hong MC, Kim SY, Bae H. Ginsenoside Rg1 enhances CD4(+) T-cell activities and modulates Th1/Th2 differentiation. Int Immunopharmacol 2004;4:235–44.
[53] He LX, Ren JW, Liu R, Chen QH, Zhao J, Wu X, Zhang ZF, Wang JB, Pettinato G, Li Y. Ginseng (*Panax ginseng* Meyer) oligopeptides regulate innate and adaptive immune responses in mice via increased macrophage phagocytosis capacity, NK cell activity and Th cells secretion. Food Funct 2017;8:3523–32.
[54] Bae M, Jang S, Lim JW, Kang J, Bak EJ, Cha JH, Kim H. Protective effect of Korean Red Ginseng extract against *Helicobacter pylori*-induced gastric inflammation in *Mongolian gerbils*. J Ginseng Res 2014;38:8–15.
[55] Choi Y-H, Kim S-E, Huh J, Han Y-H, Lee M-J. Antibacterial and antioxidative activity of roasted coffee and red ginseng mixture extracts. J Kor Soc Food Sci Nutr 2012;41:320–6.
[56] Na S, Kim JH, Rhee YK, Oh SW. Enhancing the antimicrobial activity of ginseng against *Bacillus cereus* and *Staphylococcus aureus* by heat treatment. Food Sci Biotech 2018;27:203–10.
[57] Bassetti M, Vena A, Croxatto A, Righi E, Guery B. How to manage *Pseudomonas aeruginosa* infections. Drugs Context 2018;7:212527.
[58] Wu H, Lee B, Yang L, Wang H, Givskov M, Molin S, Høiby N, Song Z. Effects of ginseng on *Pseudomonas aeruginosa* motility and biofilm formation. FEMS Immunol Med Microbiol 2011;62:49–56.
[59] Lim DS, Bae KG, Jung IS, Kim CH, Yun YS, Song JY. Anti-septicaemic effect of polysaccharide from *Panax ginseng* by macrophage activation. J Infect 2002;45:32–8.
[60] Sung WS, Lee DG. The combination effect of Korean red ginseng saponins with kanamycin and cefotaxime against methicillin-resistant *Staphylococcus aureus*. Biol Pharm Bull 2008;31:1614–7.
[61] Lee K, Kim W, Kim HJ, Kim KT, Paik H-D. Antibacterial activity of ginseng (*Panax ginseng* C. A. Meyer) stems–leaves extract produced by subcritical water extraction. Int J Food Sci Technol 2013;48.
[62] Nguyen CT, Luong TT, Lee SY, Kim GL, Kwon H, Lee HG, Park CK, Rhee DK. Panax ginseng aqueous extract prevents pneumococcal sepsis *in vivo* by potentiating cell survival and diminishing inflammation. Phytomedicine 2015;22:1055–61.
[63] Xue P, Yao Y, Yang XS, Feng J, Ren GX. Improved antimicrobial effect of ginseng extract by heat transformation. J Ginseng Res 2017;41:180–7.
[64] Riaz M, Rahman NU, Zia-Ul-Haq M, Jaffar HZ, Manea R. Ginseng: a dietary supplement as immune-modulator in various diseases. Trends in Food Sci Technol 2019;83:12–30.
[65] Lee JS, Hwang HS, Ko EJ, Lee YN, Kwon YM, Kim MC, Kang SM. Immunomodulatory activity of red ginseng against influenza A virus infection. Nutrients 2014;6:517–29.
[66] Lee JH, Min DS, Lee CW, Song KH, Kim YS, Kim HP. Ginsenosides from Korean Red Ginseng ameliorate lung inflammatory responses: inhibition of the MAPKs/NF-κB/c-Fos pathways. J Ginseng Res 2018;42:476–84.
[67] Quan FS, Compans RW, Cho YK, Kang SM. Ginseng and Salviae herbs play a role as immune activators and modulate immune responses during influenza virus infection. Vaccine 2007;25:272–82.
[68] Sung H, Kang SM, Lee MS, Kim TG, Cho YK. Korean red ginseng slows depletion of CD4 T cells in human immunodeficiency virus type 1-infected patients. Clin Diagn Lab Immunol 2005;12:497–501.
[69] Jeong JJ, Kim B, Kim DH. Ginsenoside Rb1 eliminates HIV-1 (D3)-transduced cytoprotective human macrophages by inhibiting the AKT pathway. J Med Food 2014;17:849–54.
[70] Mohebbi A, Lorestani N, Tahamtan A, Kargar NL, Tabarraei A. An Overview of hepatitis B virus surface antigen secretion inhibitors. Front Microbiol 2018;9.662-662.
[71] Lee JS, Lee YN, Lee YT, Hwang HS, Kim KH, Ko EJ, Kim MC, Kang SM. Ginseng protects against respiratory syncytial virus by modulating multiple immune cells and inhibiting viral replication. Nutrients 2015;7:1021–36.
[72] Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. J Fungi (Basel) 2017;3.
[73] Trammell RA, Cox L, Pikora J, Murphy LL, Toth LA. Evaluation of an extract of North American ginseng (*Panax quinquefolius* L.) in *Candida albicans*-infected complement-deficient mice. J Ethnopharmacol 2012;139:414–21.
[74] Sung WS, Lee DG. *In vitro* candidacidal action of Korean red ginseng saponins against *Candida albicans*. Biol Pharm Bull 2008;31:139–42.
[75] Cho A, Roh YS, Uyangaa E, Park S, Kim JW, Lim KH, Kwon J, Eo SK, Lim CW, Kim B. Protective effects of red ginseng extract against vaginal herpes simplex virus infection. J Ginseng Res 2013;37:210.
[76] Liu T, Zhao L, Zhang Y, Chen W, Liu D, Hou H, Ding L, Li X. Ginsenoside 20(S)-Rg3 targets HIF-1α to block hypoxia-induced epithelial-mesenchymal transition in ovarian cancer cells. PLoS One 2014;9:e103887.
[77] Lü JM, Weakley SM, Yang Z, Hu M, Yao Q, Chen C. Ginsenoside Rb1 directly scavenges hydroxyl radical and hypochlorous acid. Curr Pharm Des 2012;18:6339–47.
[78] Boo Y-JP, Joong-Min, Kim Jin, Suh Sung-Ock. Prospective study for Korean Red Ginseng extract as an immune modulator following a curative surgery in patients with advanced colon cancer. J Ginseng Res 2007;31:54–9.
[79] Yun TK, Choi SY, Yun HY. Epidemiological study on cancer prevention by ginseng: are all kinds of cancers preventable by ginseng? J Korean Med Sci 2001;16:S19.
[80] Bowie LE, Roscoe WA, Lui EM, Smith R, Karlik SJ. Effects of an aqueous extract of North American ginseng on MOG(35-55)-induced EAE in mice. Can J Physiol Pharmacol 2012;90:933–9.
[81] Lee MJ, Jang M, Choi J, Chang BS, Kim DY, Kim SH, Kwak YS, Oh S, Lee JH, Chang BJ, et al. Korean Red Ginseng and ginsenoside-Rb1/-Rg1 alleviate experimental autoimmune encephalomyelitis by suppressing Th1 and Th17 cells and upregulating regulatory T cells. Mol Neurobiol 2016;53:1977–2002.
[82] Jhun J, Lee J, Byun JK, Kim EK, Woo JW, Lee JH, Kwok SK, Ju JH, Park KS, Kim HY, et al. Red ginseng extract ameliorates autoimmune arthritis via regulation of STAT3 pathway, Th17/Treg balance, and osteoclastogenesis in mice and human. Mediators Inflamm 2014;2014:351856.
[83] Yu X, Zhang N, Lin W, Wang C, Gu W, Ling C, Feng Y, Su Y. Regulatory effects of four ginsenoside monomers in humoral immunity of systemic lupus erythematosus. Exp Ther Med 2018;15:2097–103.
[84] Coffman RL, Sher A, Seder RA. Vaccine adjuvants: putting innate immunity to work. Immunity 2010;33:492–503.
[85] Kim JE, Monmai C, Rod-In W, Jang AY, You SG, Lee SM, Jung SK, Park WJ. Co-immunomodulatory activities of anionic macromolecules extracted from *Codium fragile* with red ginseng extract on peritoneal macrophage ofimmune-suppressed mice. J Microbiol Biotechnol 2020;30:352–8.
[86] Kim H, Jang M, Kim Y, Choi J, Jeon J, Kim J, Hwang YI, Kang JS, Lee WJ. Red ginseng and vitamin C increase immune cell activity and decrease lung

inflammation induced by influenza A virus/H1N1 infection. J Pharm Pharmacol 2016;68:406–20.
[87] Zhang W, Cho SY, Xiang G, Min KJ, Yu Q, Jin JO. Ginseng berry extract promotes maturation of mouse dendritic cells. PLoS One 2015;10:e0130926.
[88] Zhai L, Wang Y, Yu J, Hu S. Enhanced immune responses of chickens to oral vaccination against infectious bursal disease by ginseng stem-leaf saponins. Poult Sci 2014;93:2473–81.
[89] Maqbool B, Wang Y, Cui X, He S, Guan R, Wang S, Wang Y, Hu S. Ginseng stem-leaf saponins in combination with selenium enhance immune responses to an attenuated pseudorabies virus vaccine. Microbiol Immunol 2019;63:269–79.
[90] Song X, Bao S, Wu L, Hu S. Ginseng stem-leaf saponins (GSLS) and mineral oil act synergistically to enhance the immune responses to vaccination against foot-and-mouth disease in mice. Vaccine 2009;27:51–5.
[91] Zhai L, Li Y, Wang W, Wang Y, Hu S. Effect of oral administration of ginseng stem-and-leaf saponins (GSLS) on the immune responses to Newcastle disease vaccine in chickens. Vaccine 2011;29:5007–14.
[92] Qu DF, Yu HJ, Liu Z, Zhang DF, Zhou QJ, Zhang HL, Du AF. Ginsenoside Rg1 enhances immune response induced by recombinant *Toxoplasma gondii* SAG1 antigen. Vet Parasitol 2011;179:28–34.
[93] Su F, Yuan L, Zhang L, Hu S. Ginsenosides Rg1 and Re act as adjuvant via TLR4 signaling pathway. Vaccine 2012;30:4106–12.
[94] Sun J, Song X, Hu S. Ginsenoside Rg1 and aluminum hydroxide synergistically promote immune responses to ovalbumin in BALB/c mice. Clin Vaccine Immunol 2008;15:303–7.
[95] Yang Z, Chen A, Sun H, Ye Y, Fang W. Ginsenoside Rd elicits Th1 and Th2 immune responses to ovalbumin in mice. Vaccine 2007;25:161–9.
[96] Song X, Chen J, Sakwiwatkul K, Li R, Hu S. Enhancement of immune responses to influenza vaccine (H3N2) by ginsenoside Re. Int Immunopharmacol 2010;10:351–6.
[97] Takei M, Tachikawa E, Hasegawa H, Lee JJ. Dendritic cells maturation promoted by M1 and M4, end products of steroidal ginseng saponins metabolized in digestive tracts, drive a potent Th1 polarization. Biochem Pharmacol 2004;68:441–52.
[98] Sun J, Hu S, Song X. Adjuvant effects of protopanaxadiol and protopanaxatriol saponins from ginseng roots on the immune responses to ovalbumin in mice. Vaccine 2007;25:1114–20.
[99] Zhu F, Liu X, Sun Z, Yu C, Liu L, Yang S, Li B, Wei K, Zhu R. Immune-enhancing effects of Taishan *Pinus massoniana* pollen polysaccharides on DNA vaccine expressing *Bordetella avium* ompA. Front Microbiol 2016;7:66.
[100] Hwang S-H, Shin M-S, Yoon TJ, Shin K-S. Immunoadjuvant activity in mice of polysaccharides isolated from the leaves of *Panax ginseng* C. A. Meyer. Int J Biol Macromol 2018;107:2695–700.