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Review Article

Ginsenosides are active ingredients in *Panax ginseng* with immunomodulatory properties from cellular to organismal levels

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ABSTRACT

The immune system is one of the most important parts of the human body and immunomodulation is the major function of the immune system. In response to outside pathogens or high inflammation, the immune system is stimulated or suppressed. Thus, identifying effective and potent immunostimulants or immunosuppressants is critical. Ginsenosides are a type of steroid saponin derived from ginseng. Most are harmless to the body and even have tonic effects. In this review, we mainly focus on the immunostimulatory and immunosuppressive roles of two types ginsenosides: the protopanaxadiol (PPD)-type and protopanaxatriol (PPT)-type. PPT-type ginsenosides include Rg1, Rg2, Rh4, Re and notoginsenoside R1, and PPD-type ginsenosides include Rg3, Rh2, Rb1, Rb2, Rc, Rd, compound K (CK) and PPD, which activate the immune responses. In addition, Rg1 and Rg6 belong to PPT-type ginsenosides and together with Rg3, Rb1, Rd, CK show immunosuppressive properties. Current explorations of ginsenosides in immunological areas are in the preliminary stages. Therefore, this review may provide some novel ideas to researchers who study the immunoregulatory roles of ginsenosides.

1. Introduction

After the worldwide pandemic caused by COVID-19, increasing numbers of people have realized that innate body immunity is the first barrier to safeguard their health. Thus, boosting human immunity is an important issue. Immunity is the body's ability to defend against the invasion of outside pathogens including virus, bacteria, or other microorganisms. Of course, for general people, immune boosting is a common saying in immune system in the narrower sense. There are two types of immunity, innate immunity and adaptive immunity [1]. Innate immunity is considered to be the first barrier of defense against pathogens, though this kind of protection is fundamental [2]. Adaptive immunity is activated when innate immunity is insufficient against the pathogen. Therefore, adaptive immunity is more specific than the innate component [3]. The adaptive immune response is mainly carried out by two kinds of specialized cells, T-cells and B-cells. T-cells are in charge of the cell-mediated immune response, whereas B-cells control the humoral immune response [3]. Although adaptive immunity can specifically attack pathogens, this kind of response takes three to five days, even weeks, to produce sufficient lymphocytes to kill the pathogens. If there is no innate response, most pathogens have enough time to damage the host during this period. Because innate immunity can be rapidly activated, control the infection, and gather pathogen information, it is considered as the one of main protective functions in the immune system [1–4]. The role of memory in adaptive immunity can prevent re-infection in the long term. If the host is exposed to the same type of pathogen, the adaptive immunity can respond and quickly eliminate the threat [3,5].

The response of the immune system can categorized into two categories: immunostimulatory (increasing immunity) and immunosuppressive (decreasing immunity) response [6]. Immunostimulatory activity means that the immune response is enhanced against many disorders, such as infection of pathogenic microorganisms, immunodeficiency or even cancers [7–9]. Many drugs, called immunostimulants, such as lipopolysaccharides (LPS), can up-regulate the immune system. LPS is present in almost all

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Gram-negative bacteria. It is one of the exceedingly strong activators for innate immunity that rapidly activates macrophages and B lymphocytes [10–12]. The main functions of immunostimulants are to induce the immune system of humans and animals to improve the body's resistance and prevent disease.

Drugs that down-regulate the immune responses are called immunosuppressants. As the name suggests, immunosuppressants inhibit the immune response and are prescribed to prevent immune rejection in organ or tissue transplantation and to treat autoimmune diseases such as allergies, pemphigus, and lupus [6,13–15]. For example, glucocorticoids have been used in the clinic for many years and show a high success in treating acute immune rejection of organ transplants or severe autoimmune disorder [15–17]. They act as transcription factors to directly bind to DNA through combining with receptors and also bind and interfere with other transcription factors [18]. Immunomodulation drugs contain immunostimulants and immunosuppressants, which have their own capabilities. To maintain homeostasis or return to a normal state, suitable immunostimulants or immunosuppressants must be selected and administered.

As more and more immunomodulators have been discovered, researchers found that these immunomodulators have numerous functions. To study the mechanisms of immunomodulation, multiple cells that are related with immune systems have been studied. These cells include neutrophils, monocytes or macrophages, and lymphocytes, which include T-cells, B-cells and natural killer (NK) cells [19,20]. Neutrophils, namely human neutrophilic polymorphonuclear leukocytes [21], are produced in the bone marrow and are located in the bloodstream to provide a potent defense against infections through rapidly migrating to the sites of infections [21–23]. Neutrophils are a pivotal component in the immune response that not only recruit, activate, and program antigen-presenting cells (APCs), but also produce tumor-necrosis factor (TNF) and other cytokines such as interleukin (IL)-1α, IL-1β, and IL-6 to stimulate the differentiation and activation of dendritic cells (DCs) and macrophages [23,24]. Neutrophils have a close relationship with monocytes and macrophages. Monocytes are derived from peripheral blood mononuclear cells (PBMCs). They also shift in the bloodstream and capture the pathogenic microorganisms. Once macrophages mature and migrate into tissues, they differentiate into DCs and macrophages [25,26]. As the first barrier to defend against pathogens, macrophages ingest microorganisms and directly deliver noxious components outside [27]. Lymphocytes are also extremely crucial immune cells in the immune system. They are developed from stem cells that are located in the bone marrow and work in the blood and lymph tissues. If these cells move to the thymus, they become T-cells. Lymphocytes that remain in the bone marrow are called B-cells [28,29]. Based on their functions, T-cells are classified into three types: helper T-cells, killer T-cells, and regulatory T-cells. These cells express different cell surface proteins, CD4, CD8 and CD4 FOXP3 [30–32]. B-cells also have three subsets, which includes B-1, follicular and marginal zone B cells. Depending on the condition, they can be activated in the presence or the absence of T-cells [33]. NK cells, which comprise a minor part of total lymphocytes, are distributed in both lymphoid and nonlymphoid tissues [31,34]. Based on the difference of homing properties, NK cells in humans are divided into two subsets, $CD56^{dim}$ and $CD56^{bright}$.

We next discuss the immune system based on its different components, including white blood cells, antibodies, complement system, lymphatic system, spleen, bone marrow, and thymus. White blood cells are the crucial player in our immune system. They are produced by the thymus and contain two main types, granulocytes and agranulocytes. Granulocytes include neutrophils, eosinophils and basophils, and agranulocytes include lymphocytes and monocytes [35]. Neutrophils are the major component of our white blood cells and play a role as body scavengers that get rid of many bacteria and fungus. Eosinophils respond to a variety of infection and inflammation and basophils are highly present in the allergic reaction. The function of monocytes is to target and fight off chronic infections.

Immune antibodies come from T-cells and B-cells. They recognize the antigens produced by outside microbes or toxins. Once the antibodies find the invader, the cells will quickly defend against the threat. Vaccines are designed based on this mechanism. Vaccines stimulate our immune system and produce antibodies. There are five major immunoglobulins (Ig) antibodies: IgA, IgG, IgM, IgD and IgE. These antibodies are all generated by B cells. IgA, IgM and IgG are commonly used in diagnosis. When our bodies are infected by organisms, IgA and IgM are quickly made by our immune systems and act as the earliest antibodies to defend or delay the infection. Within several weeks, IgG is produced in our immune system, and IgA and IgM are gradually broken down. Thus, IgA and IgM act in the short-term whereas IgG are involved in a long-lasting response. The complement system consists of some proteins that complement the functions of antibodies.

The lymphatic system contains lymph nodes, lymph vessels and lymphocytes [36]. During infection, lymph nodes can catch the microbes. Lymphocytes are carried by lymph vessels to fight against the infection. The spleen acts as a filter of blood to removes damage and bone marrow serves as a factory to produce red blood cells, white blood cells and platelets [37].

Ginseng is a traditional herb that has been used for various conventional medical therapies for more than 5000 years. Historically, people believed that ginseng could prolong human life. Current studies have shown that ginseng exhibits multiple therapeutic properties against various diseases, like physical and infectious diseases and diverse cancers. Ginseng includes *Panax ginseng* Meyer (Korean ginseng), *P. quinquefolius* L. (American ginseng), *P. japonicus* Meyer (Japanese ginseng) and *P. notoginseng* (Burk) F.H. Chen (Sanqi-ginseng) [38,39]. Korean ginseng is the most studied and widely used in all over the world, and its roots are a main focus of research [40,41]. Based on the water content and processing method, Korean ginseng, especially the roots, can be categorized as fresh ginseng, white ginseng and red ginseng [42]. Red ginseng is incubated in 100 °C steam for more than 2 h until the moisture content is less than 15%.

Ginsenosides, which belong to steroid saponins, are the major components of ginseng. Over 100 ginsenosides have been separated from the extractions. These ginsenosides are named as Rx: the 'x' represents the polarity of each ginsenoside on the thin-layer chromatography, in which the most polar component is named as Ra, while the least polar one is addressed as Rh [42]. According to the difference of backbone [43], ginsenosides can be classified into four types, the PPD-, PPT-, ocotillol- and oleanolic acid-types (Fig. 1). PPD-type ginsenosides include Ra1, Ra2, Ra3, Rb1, Rb2, Rb3, Rc, Rd, F2, Rg3, Rg5, Rh2, Rh3, CK and PPD. PPT-type ginsenosides include Re, Rg1, Rg2, Rg4, Rh1, Rh4, Rf and PPT [44–46]. Ocotillol-type ginsenosides contain 24(R)-pseudoginsenoside-F11, 24(R)-pseudoginsenoside-RT5, Majonoside R1 and R2 [47], and Ro is an oleanolic acid-type ginsenoside.

Ginseng has been used as an immunomodulatory herb for a long time. Ginseng is used to reduce inflammation induced by infection by outside microorganisms and can also be applied for boosting human immunity. However, these activities are not paradoxical. Because of its complicated properties, ginseng has attracted attention from researchers. However, the immunoregulatory role of ginseng is not well understood. Thus, in this review, we specifically focus on the immunomodulatory roles of ginsenosides and discuss the functions of ginsenosides from the cell to body levels. Other

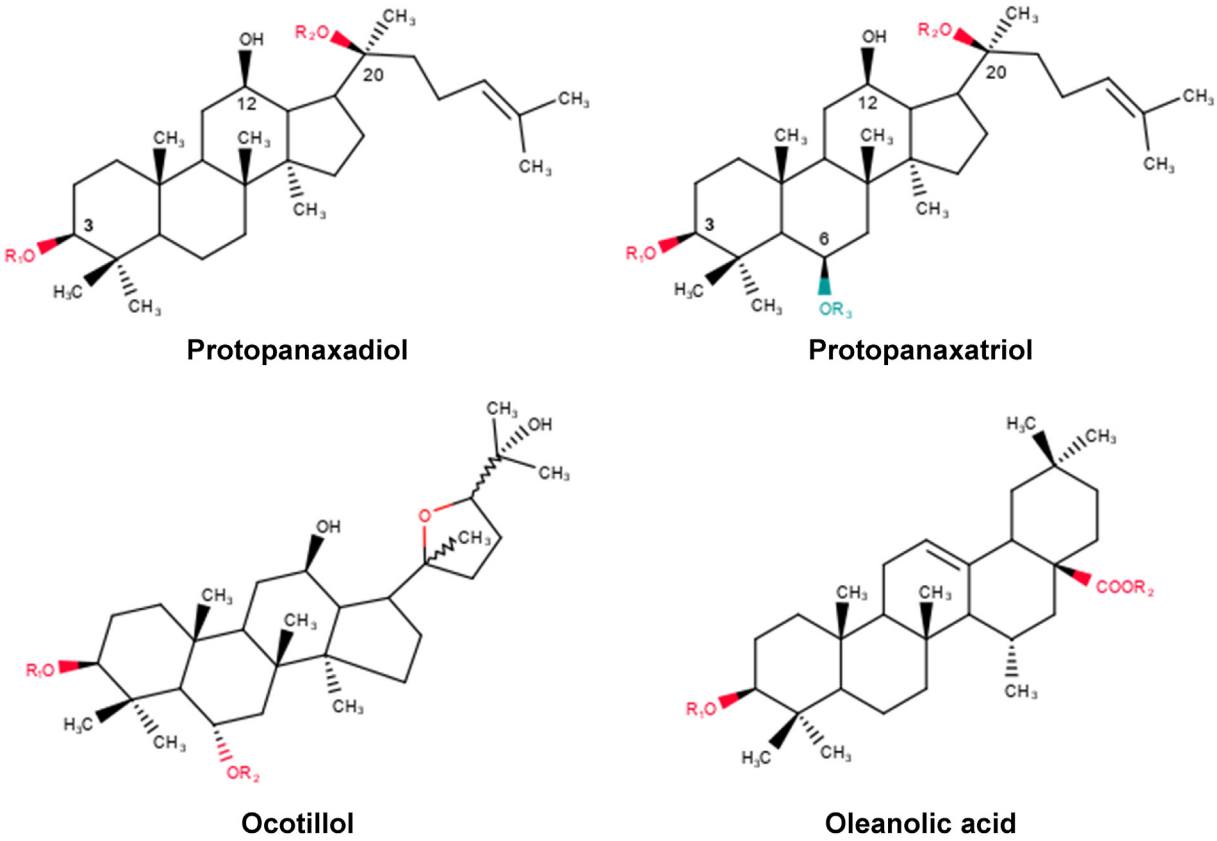

Fig. 1. Types of ginsenosides.

components have similar functions such as ginseng polysaccharides. The use of ginsenosides as immunomodulators may be useful for further studies and also as a guideline for commercial development.

2. Main body

2.1. The immunostimulatory role of ginsenosides

In research on the immunostimulatory functions of some drug, the Th1 and Th2 responses will be considered. Th1 and Th2 are T helper type 1 and 2, respectively, which are associated with helper T-cells. Helper T-cells are the T lymphocytes that express CD4. The Th1 immune response is also called cellular immune response. In the Th1 response, Th1 cells act as an activator to enhance human immunity and induce phagocyte-dependent inflammation [48]. The Th2 response, also known as the humoral immune response, is related with the promotion of the responses of antibody like immunoglobulin E (IgE) and the accumulation of eosinophils, as well as inactivation of phagocytic cells [48]. Th1 cells secrete interferon (IFN)-γ, IL-2 and TNF-β, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-13 and other cytokines. Because of this, Th2 is mostly like to counteract excessive Th1 response, which will cause uncontrolled damage [49]. In the investigation of immunostimulatory roles of ginsenosides, more attention can be paid to the relationships between ginsenosides and Th1 and Th2 responses.

2.1.1. The mechanisms of immunostimulatory role of ginsenosides in vitro

As one of the most important components in ginseng, ginsenosides are a focus of much attention. Previously, ginseng was known to boost human immunity. However, research is ongoing into the mechanisms of the immunostimulatory role of ginseng. Therefore, the ginsenosides have been isolated and studied. Shin et al. compared the immune stimulating role of white ginseng and heat-processed ginseng (HPG) and found that HPG, which contains Rg3, Rg5 and Rk1 complex, can enhance the activation of macrophages through inducing the mitogen-activated protein kinase (MAPK)/activator protein 1 (AP-1) and nuclear factor-κB (NF-κB) signaling pathways, as indicated in Fig. 2. In addition, they found that extracellular signal-regulated kinase (ERK)/c-Jun is the main mechanism for this activation and the cytokines TNF-α and IL-6 were produced [50]. Rg3 was also studied for its effects in macrophage phagocytosis. Rg3 promotes phagocytosis of IgG-opsonized *Escherichia coli* and IgG-opsonized beads (IgG beads) through activating ras-related C3 botulinum toxin substrate 1 (Rac1) and cell division cycle 42 (CDC42) and up-regulating the phosphorylation of ERK and p38 MAPK. IL-6 and TNF-α were also induced [51]. Kim et al. compared red ginseng (RG) and fermented RG (FRG) and found that the content of Rd, Rh1, F2 and Rg3 were increased. FRG up-regulated the activity of macrophages much more significantly than RG through MAPK and NF-κB pathways. In addition, FRG can boost the immunostimulatory function in central immune cells which contains mouse splenocytes and bone marrow-derived macrophages by promoting the proliferation and production of TNF-α and IL-6 [52]. Another two PPD-types ginsenosides, 20S-dihydroprotopanaxadiol (2H-PPD) and CK, reported by Kim et al. [53] and Yang et al. [54] respectively, showed an immunostimulatory role on the innate immune response. Both activate monocytes and macrophages through increasing phagocytic uptake, cell to cell aggregation, and the surface level of costimulatory molecules CD80 and CD86. Surface level CD43 was also enhanced by these two

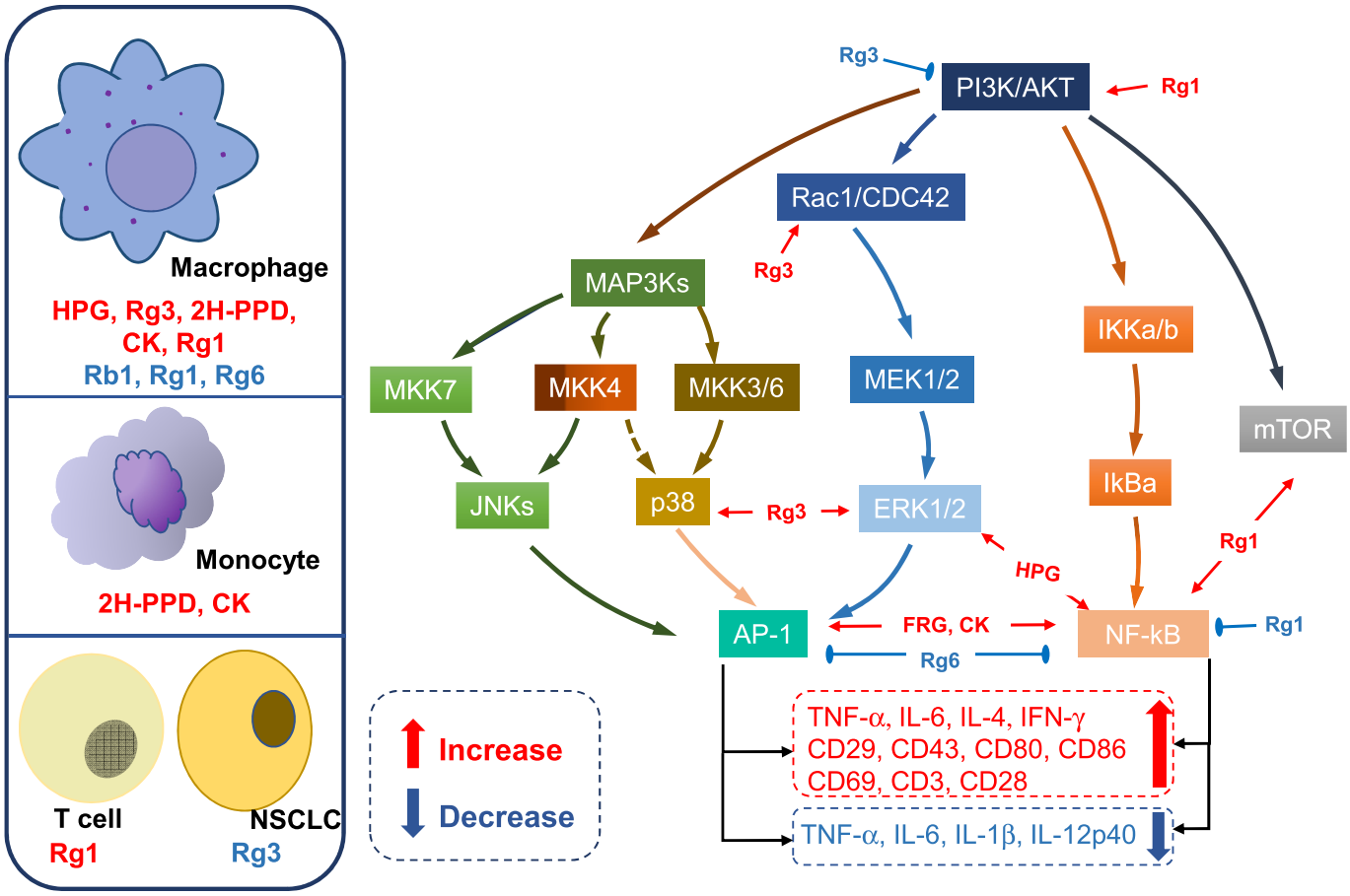

Fig. 2. The immunomodulatory role of ginsenosides *in vitro*.

compounds whereas CD29 was increased by 2H-PPD. Some cytokines such as TNF-α can be promoted by CK through NF-κB and AP-1 pathways. However, 2H-PPD cannot induce the adhesion of cells to the extracellular matrix and CK suppressed the interactions of cell to tissue. CD82, which is the marker of monocyte differentiation, was also inhibited by CK.

Although most *in vitro* experiments were performed by PPD-type ginsenosides, some other ginsenoside which derived from PPT-type were also used *in vitro*. Rg1, which is a major component of PPT-type ginsenoside, was studied by Wang et al. [55]. Rg1 can dramatically boost the innate immune response in macrophages. In response to LPS-activated macrophages, Rg1 enhanced the production of TNF-α through up-regulating phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling pathways and down-regulating the secretion of IL-6 via suppressing the NF-κB pathway. In addition, Rg1 was also tested in the splenocytes of BALB/c mice to find the mechanisms of enhancement of activity of $CD4^+$ T cells [56]. Rg1 increased the immune activity of $CD4^+$ T cells through accelerating their proliferation. This activation owed to the enhancements of CD3, CD28 and CD69. Apart from that, Rg1 suppressed the Th1 immune response by restraining IFN-γ whereas enhance the Th2 response by increasing IL-4 in purified $CD4^+$ T cells, which adjusted the balance of Th1 and Th2 and corrected the Th1-dominant pathological disorders (Table 1).

2.1.2. The immunostimulatory applications of ginsenosides in vivo

2.1.2.1. The immunostimulatory mechanism of PPT-type ginsenoside in vivo. As a natural tonic herb, ginseng has been used as an immune booster for more than thousands of years. Ginsenosides, the major component of ginseng, has been tested in many animal models for research on their mechanisms of immunomodulatory action (Fig. 3A). Currently, the major role of ginsenosides is acting as adjuvant, as well as a few cases were still applied *in vivo* alone. Rg1 was used as adjuvant in BALB/c mice. Sun et al. screened many ginsenosides containing both PPT- and PPD-types and found that Rg1 is the most potent and ideal adjuvant that when co-administrated with ovalbumin (OVA) exhibited immunostimulatory properties [57]. Combining Rg1 with OVA caused a huge promotion of IgG1 and IgG2a in mouse blood and led to a great proliferation of lymphocytes. All the enhancements are ascribable to IL-5/IFN-γ production and Th1/Th2 activation. Rg2 and Re also exhibited similar characteristics as Rg1v [57]. Sun et al. investigated co-treatment of Rg1 and aluminum hydroxide to check the immune response to OVA [58]. Similar results were obtained as well as delayed-type hypersensitivity and less hemolytic activity. Another study in BALB/c mice examined co-treatment Rg1 with hepatitis B surface antigen (HBsAg) [59]. Rg1 not only increased the Th1 responses including IgG2b and IFN- γ but also enhanced the Th2 responses containing IgG1 and IL-4 through TLR4 signaling pathway. Qu et al. and Su et al. also studied the Rg1 combination with *T. gondii* recombinant surface antigen 1 (rSAG1) and inactivated porcine reproductive and respiratory syndrome virus (PRRSV) vaccine, respectively, in ICR mice. Co-administration of Rg1 and rSAG1 significantly enhanced the activities of NK cells and T helper cells and stimulated higher expressions of IL-4 and IFN- γ, which indicating the promising adjuvant together with rSAG1 against toxoplasmosis [60]. PRRSV vaccine combined with Rg1

Table 1
The immunomodulatory role of ginsenosides *in vitro*.

The immunostimulatory role of ginsenosides *in vitro*					
Type of ginsenosides	Ginsenosides	Target cells	Signaling pathways	Cytokine/molecules	Ref.
	FRG (Rd, Rh1, F2)	Macrophages Splenocytes	MAPKs NF-κB	TNF-α↑ IL-6↑	[52]
PPD-type	HPG (Rg3, Rg5, Rk1)	Macrophages	MAPKs/AP-1 NF-κB	TNF-α↑ IL-6↑	[50]
	Rg3	Macrophages	Rac1/CDC42 ERK1/2 and p38	TNF-α↑ IL-6↑	[51]
	2H-PPD	Macrophages Monocytes		CD29, CD43↑ CD80, CD86↑	[53]
	CK	Macrophages Monocytes	AP-1 NF-κB	CD43, CD69↑ CD80, CD86↑ TNF-α↑	[54]
PPT-type	Rg1	Macrophages	NF-κB PI3K/AKT/mTOR	TNF-α↑ IL-6↑	[55]
		T helper cells		IL-6, IL-4↑ CD3, CD28, CD69↑	[56]
The immunosuppressive role of ginsenosides *in vitro*					
PPD-type	6″-*O*-acetylginsenoside Rb1	Macrophages		TNF-α↓ IL-6↓	[82]
	Rg3	NSCLC cells	AKT, ERK and NF-κB/HIF-1α		[83]
PPT-type	Rg1	Macrophages	NF-κB	TNF-α↓ IL-6↓	[79]
	Rg6	BMDMs	NF-κB MAPKs	TNF-α, IL-1β↓ IL-12p40↓ IL-6↓	[81]

activated IgG and IgA antibodies and neutralizing antibody titer, increased the proliferation of T and B lymphocytes as well as the CD107a expression in $CD4^+$ T cells. In addition, many cytokines which related to Th1 (IFN-γ and IL-2), Th2 (IL-5 and IL-10), and Th17 (IL-6 and IL-17A) were accumulated by stimulating type I interferon signaling pathway [61]. Chickens can also be used to test the association of Rg1 and infectious bursal disease vaccine. These chickens underwent the oxidative stress which caused by cyclophosphamide (CP). This combination not only relieved the oxidative stress but also raised the proliferation of lymphocyte and the cytokines of immune response like IFN-γ and IL-6 [62].

We previously introduced Rg1, which acts as an adjuvant against OVA in BALB/c mice. Another animal model, ICR mice, was used to examine the immune response against OVA together with various ginsenosides, such as Re, notoginsenoside R1 and Rh4 [63,64]. Similar to Rg1, these three ginsenosides dramatically promoted the proliferation of splenocytes induced by concanavalin A (Con A), LPS and OVA. Additionally, the specific antibodies IgG, IgG1 and IgG2b were also increased in serum. Moreover, there were none or low hemolytic effects of these three ginsenosides, indicating they show safe properties as an adjuvant.

Several vaccines were tested on the ICR mice with the addition of Re. H3N2, an inactivated influenza virus antigen, is one of the vaccines was evaluated together with Re. IgG, IgG1, IgG2a, IgG2b and HI titers, which were derived from serum, were significantly amplified. Both Th1 and Th2 cytokines IFN-γ and IL-5 were highly secreted with the proliferation of lymphocytes, which showed mixed immune responses for enhancing the activities of vaccine [65]. Two other studies examined recombinant *Toxoplasma gondii* ROP18 antigen [66] and inactivated rabies virus vaccine (RV) [67]. Beside the enhancements of IgG production and Th1/Th2 cytokines (IFN-γ, IL-4, IL-10 and IL-12), RV vaccine with Re significantly increased the ratio of $CD4^+$ and $CD8^+$. These studies demonstrated that PPT-type ginsenoside can improve the efficiency of vaccines in activating the immune responses of Th1 and Th2.

2.1.2.2. The immunostimulatory mechanism of PPD-type ginsenoside in vivo. Rg3 effectively induces macrophage phagocytosis in mouse lung through activating the phosphorylation of ERK1/2 and p38 [51], and also significantly promotes the cellular immunity of KM mice that were transplanted with the hepatocellular carcinoma cell line H22 [68]. After Rg3 treatment, lymphocytes induced by Con A were highly proliferated and two cytokines, IFN-γ and IL-2, which derived from the Th1 immune response, were accumulated (Fig. 3A). This immunostimulatory role caused the suppression of xenografted H22 tumors could provide guidance for clinical tumor immunity. CP is a chemotherapeutic agent that caused immune suppression. With CP injury, macrophage phagocytosis is inhibited by decreased activities of lactate dehydrogenase and acid phosphatase as well as the production of IgG, IL-2 and granulocyte colony-stimulating factor. In addition, the disordered balance of Th1 and Th2 resulted from the suppression of T-Cell-Specific T-Box Transcription Factor T-bet and IFN-γ and the enhancement of *trans*-acting T-cell-specific transcription actor GATA-3 and IL-4. Rg3 partially recovered the immunity of immunodeficient BALB/c mice caused by CP, including the activation of macrophages and T cells as well as the balance of the Th1 and Th2 immune response [69]. Although CP is used to treat non-small cell lung cancer (NSCLC) as a chemotherapeutic drug, it causes the severe immune suppression. Qian et al. reported that this serious immune deficiency can be improved by Rh2 through down-regulation of fatty acid metabolism [70]. Rh2 induced the oxidative decomposition of fatty acid and attenuated the protein expression of fatty acid synthase, which caused immune enhancement in CP-treated mice.

Interestingly, Rh2 also showed a similar immune response against tumor [71]. Wang et al. established a melanoma C57BL/6 mouse model by injecting B16F10 melanoma cells. The administration of Rh2 caused inhibition of tumor growth and induced the infiltration of $CD4^+$ and $CD8^+$ lymphocytes. Rh2 increased the cytotoxicity of lymphocytes to suppress B16F10 cells, which promotes the immunological response against melanoma.

In screening the effects that enhance the immune responses to OVA in BALB/c mice, some PPD-type ginsenosides like Rg3 and Rb1 also displayed properties of immunostimulants [57,72]. Song et al. co-administered the nanoparticles of PPD-type ginsenosides (Rb2, Rc, Rb1 and Rd) with OVA in ICR mice [73]. Compared with OVA

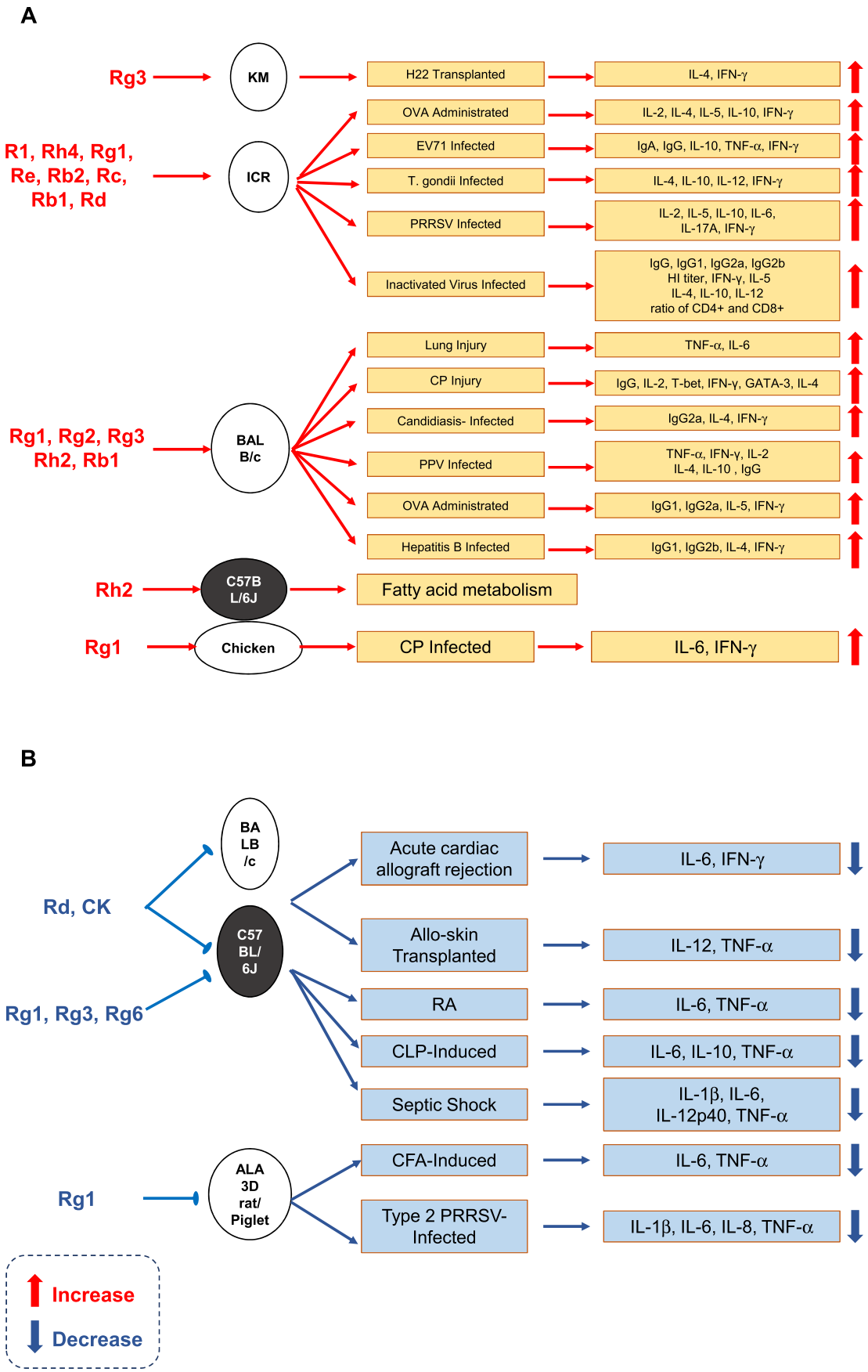

Fig. 3. The immunomodulatory role of ginsenosides *in vivo*. (A) The immunostimulatory mechanism of PPT- and PPD-type ginsenosides *in vivo*. (B) The immunosuppressive mechanism of PPT- and PPD-type ginsenosides *in vivo*.

administration alone, co-treatment these PPD-type nanoparticles can remarkably enhance the levels of IgG1, IgG2a, IgG2b and IgG3. In addition, the proliferation of B and T lymphocytes was accelerated. The productions of cytokines IFN-γ and IL-5, which belongs to Th1 and Th2 immune responses, were also higher than those with OVA injected alone. Yang et al. reported that Rd not only can increase the cytokines above, but it also can induce the expressions of IL-2, IL-4 and IL-10 in ICR mice to resist OVA [74]. Han et al. used Rd to assist *Candida albicans* surface mannan (CASM) to produce antibody against candidiasis [75]. BALB/c mice that were intraperitoneally injected with CASM and Rd induced the Th1 immune response by strongly producing IFN-γ. Moreover, the high increase of IL-4 and the ratio of IgG2a to IgG showed the effective Th2 response, which suggested that Rd can be a useful immunostimulatory adjuvant.

Rb1 was used as an immunostimulatory adjuvant to test the porcine parvovirus (PPV) vaccine [76]. Cytokines were collected in serum or the cultured supernatants of lymphocyte of BALB/c mice and expression levels were measured by ELISA. The results demonstrated that the vaccine containing Rb1 resulted in dramatically enhanced secretion of cytokines such as TNF-α, IFN-γ, IL-2, IL-4 and IL-10 from the Th1 and Th2 immune response. These increased cytokines together with the stimulation of specific IgG1, IgG2a and IgG2b revealed that Rb1 can balance the immune response of Th1 and Th2. However, as the immunostimulatory agent, Rb1 displayed an antiviral role to treat enterovirus 71 (EV71) infection [77]. Suckling ICR mice were infected by EV71 and treated with Rb1. The results showed that Rb1 reduced the cytopathic effect and the protein level of viral protein-1 (VP-1) caused by EV71. Immune cytokines such as TNF-α, IFN-γ and IL-10 and specific antigens like IgA, IgG1 and IgG2a were significantly increased, indicating enhanced immune responses by Rb1. In addition, Rb1 strengthened the expression of IFN-β. Upon knockdown of IFN-β, VP-1 was not significantly be inhibited by Rb1 although it was remarkably suppressed by Rb1. This finding demonstrated that the antiviral function of Rb1 is directly related with host immune responses, which provides a link between immune responses and antiviral therapeutics (Table 2).

2.2. The immunosuppressive role of ginsenosides

Since the immunostimulatory mechanisms of ginsenosides both *in vitro* and *in vivo* have been introduced, next we will discuss the immunosuppressive application of each ginsenoside according to the classification. Kim et al. [43] reviewed the immunosuppressive roles of ginsenosides prior to 2016 very well. Therefore, here we summarize studies related to immunosuppression of ginsenosides from 2016 and onwards. Many studies examined both *in vitro* and *in vivo* findings and we will also combine them here (Tables 1 and 2).

2.2.1. The immunosuppressive mechanisms and applications of PPT-type ginsenosides

People with sepsis have a high mortality rate because these individuals show an unbalanced immune response and apoptotic lymphocytes. The effects of Rg1, a PPT-type ginsenoside, on sepsis C57BL/6 mice induced by cecal ligation and puncture (CLP) were examined [78]. Rg1 remarkably reversed the high expressions of TNF-α, IL-6 and IL-10 induced by CLP and limited the apoptotic splenocytes by decreasing the highly apoptotic lymphocytes in the thymus (Fig. 3B). Rg1 also inhibited the inflammation of RAW264.7 cells stimulated by LPS and relieved the damage of adjuvant-induced arthritis (AIA) 3D rats induced by Complete Freund's adjuvant (CFA) [79]. The immune cytokines (TNF-α, IL-6) and NF-κB signaling pathway were dramatically inhibited whereas the expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) was enhanced. This finding could provide good guidance for treating AIA. Additionally, Rg1 can alleviate the threat of type 2 PRRSV in piglets. Rg1 decreased the productions of cytokines (TNF-α, IL-1β, IL-6 and IL-8) and the activations of NF-κB pathway in Marc-145 cells and porcine alveolar macrophages (PAMs) infected by PRRSV. Rg1 not only relieved lung injury and virus in serum and tissues, but it also promoted the survival rate of piglets [80]. The rare ginsenoside Rg6 was also found to have immunosuppressive functions [81]. As an inhibitor of the inflammatory response of Toll-like receptor-4, Rg6 relieved septic shock in C57BL/6 mice induced by LPS and sepsis induced by CLP. Rg6 suppressed the production of TNF-α, IL-1β, IL-6 and IL-12p40 and augmented the expression of IL-10, and these results were confirmed in bone marrow-derived macrophages (BMDMs) through down-regulating NF-κB and MAPKs signaling pathways. Moreover, Rg6 triggered miR-146a, which is an operator miRNA in BMDMs with anti-inflammation functions. Hence, Rg6 elicited an immunosuppressive role through inhibiting NF-κB and MAPKs signaling pathways and stimulating IL-10 and miR-146a.

2.2.2. The immunosuppressive mechanisms and applications of PPD-type ginsenosides

The 6′′-*O*-acetylginsenoside Rb1 isolated from North American ginseng by Samimi et al. [82] showed immunosuppressive activity in LPS-induced macrophage cells. Gemcitabine (GEM) is a chemotherapeutic drug used to treat NSCLC. GEM treatment increased the expression of pentraxin (PTX)-3 in lung cancer cells. PTX-3 is an gene related to pro-inflammation and is extremely highly expressed in lung cancer cells [83]. Yan et al. discovered that Rg3 can attenuate PTX-3 induced by GEM by down-regulating AKT, ERK and NF-κB/hypoxia-inducible factor 1-alpha (HIF-1α) pathways [84]. Rg3 relieves rheumatoid arthritis (RA) in mice. C57BL/6 mice administrated with CFA exhibited severe inflammation (Fig. 3B). The highly expressed pro-inflammatory cytokines TNF-α and IL-6 induced by CFA were suppressed. Moreover, the anti-inflammatory cytokines IL-10 and TGF-β, which were inhibited by CFA, were reversed after Rg3 treatment. $CD4^{+}CD25{+}Foxp3^{+}$Treg cells were enhanced as well, which showed that Rg3 has immunosuppressive and immune tolerance effects in RA mice [85].

In some patients who receive cardiac transplantation, acute cardiac allograft rejection can occur. Acute rejection can stimulate cellular immunity, which leads to the failure of transplantation. CK, a potent immunosuppressive adjuvant, was tested by Wang et al. [86] for its ability to inhibit acute rejection in both C57BL/6 and BALB/c mice. The results showed that CK decreased the proliferation of lymphocytes. Moreover, CK dramatically inhibited the production of IL-2 and IFN-γ but not IL-10. Islet transplantation was studied by Ma et al. [87] to assess the immunosuppressive role of CK in streptozotocin (STZ)-induced diabetic mice. In addition to the suppression of the same cytokines, CK not only decreased the occupancy of $CD4^{+}$ and $CD8^{+}$ T cells in the lymphatic system, but it also enhanced the expressions of TGF-β and Foxp3, which triggered the generation of Tregs. Allo-skin transplantation was conducted by Wang et al. [88] to examine the suppression effect of Rd on skin allograft rejection. Rd exhibited a similar characteristic with CK: Rd also inhibited TNF-α, IL-12 and up-regulated IL-10, which was thought to treat Th1-related transplant rejection.

3. Discussion

The coronavirus disease-19, caused by a globally rampant virus called COVID-19, represents an ongoing threat to human health. The global pandemic has caused thousands of deaths, with impacts on the global economy, resulting in a severe recession. Researchers

Table 2
The immunomodulatory role of ginsenosides *in vivo*.

The immunostimulatory role of ginsenosides *in vivo*						
Type of ginsenosides	Ginsenosides	Applications	Animal models	Signaling pathways/ mechanisms	Cytokine/molecules	Ref.
PPD-type	Rg3	Mouse macrophages	Lung injury in BALB/c mice	ERK1/2 p38	TNF-α↑ IL-6↑	[51]
		Lymphocytes	H22 transplanted KM mice	Th1	IFN-γ↑ IL-2↑	[68]
		Mouse macrophages and Lymphocytes	CP-injury In BALB/c mice	Th1/Th2	IgG, IL-2↑ T-bet, IFN-γ↑ GATA-3↑ IL-4↑	[69]
	Rh2		CP-treated C57BL/6J BALB/c mice	Fatty acid metabolism		[70]
		Lymphocytes	B16F10-injected C57BL/6 mice	$CD4^+$ and $CD8a^+$ T-lymphocytes' infiltration		[71]
	nanoparticles (Rb2, Rc, Rb1 and Rd)	Lymphocytes	Against OVA in ICR mice	Th1/Th2	IgG↑ IFN-γ, IL-5↑	[73]
	Rd	adjuvant	Against OVA in ICR mice	Th1/Th2	IL-2, IL4↑ IL-10↑	[73]
		Adjuvant with CASM	Candidiasis-infected BALB/c mice	Th1/Th2	IFN-γ↑ IL-4, IgG2a↑	[75]
	Rb1	Adjuvant with PPV vaccine	PPV infected BALB/c mice	Th1/Th2	TNF-α, IFN-γ IL-2, IL-4, IL-10, IgG↑	[76]
		Adjuvant with EV71	EV71 infected ICR mice	Th1/Th2	TNF-α, IFN-γ, IL-10, IgA, IgG↑	[77]
PPT-type	Rg1, Rg2	Adjuvant	Against OVA in BALB/c mice	Th1/Th2	IgG1, IgG2a↑ IFN-γ, IL-5↑	[57]
	Rg1	Adjuvant with aluminum hydroxide	Against OVA in BALB/c mice	Th1/Th2	IgG1, IgG2a↑ IFN-γ, IL-5↑	[58]
		Adjuvant with HBsAg	Hepatitis B infected BALB/c mice	Th1/Th2 TLR4	IFN-γ, IgG2b↑ IL-4, IgG1↑	[59]
		Adjuvant with rSAG1	T. gondii infected ICR mice	NK cells T helper cells	IFN-γ, IL-4↑	[60]
		Adjuvant with PRRSV vaccine	PRRSV infected ICR mice	Th1/Th2/Th17 type I interferon	IFN-γ, IL-2↑ IL-5, IL-10↑ IL-6, IL-17A↑	[61]
		Adjuvant with bursal disease vaccine	CP infected chicken	Th1	IFN-γ, IL-6↑	[62]
	Notoginsenoside R1, Rh4	Adjuvant	Against OVA in ICR mice	Th1	IgG, IgG1, IgG2b↑	[63] [64]
	Re	Adjuvant with H3N2	Inactivated influenza virus infected ICR mice	Th1/Th2	IgG, IgG1, IgG2a, IgG2b, HI titer↑ IFN-γ, IL-5↑	[65]
		Adjuvant with ROP18 antigen	*Toxoplasma gondi* infected ICR mice	Th1/Th2	IFN-γ, IL-4, IL-10, IL-12↑	[66]
		Adjuvant with RV	Inactivated rabies virus infected ICR mice	Th1/Th2	IFN-γ, IL-4, IL-10, IL-12↑ ratio of $CD4^+$ and $CD8^+$ ↑	[67]
The immunosuppressive role of ginsenosides *in vivo*						
PPD-type	Rg3		C57BL/6 mice with RA	Th1	TNF-α, IL-6↓	[85]
	CK	Lymphocytes	Acute cardiac allograft rejection in C57BL/6, BALB/c mice	Th1	IL-2, IFN-γ↓	[86]
		Lymphocytes	STZ-induced diabetic mice with islet transplantation		$CD4^+$, $CD8^+$ T cells↓	[87]
	Rd		Allo-skin transplanted C57BL/6 and BALB/c mice	Th1	TNF-α, IL-12↓	[88]
PPT-type	Rg1	Lymphocytes	CLP-induced C57BL/6 induced	Th1/Th2	TNF-α, IL-6 IL-10↓	[78]
		Lymphocytes	CFA-induced AIA 3D rats	NF-κB	TNF-α IL-6↓	[79]
		Lymphocytes	type 2 PRRSV-infected piglets	Th1	TNF-α, IL-1β, IL-6, IL-8↓	[80]
	Rg6	Lymphocytes	LPS-induced C57BL/6 mice (Septic shock)	NF-κB MAPKs	TNF-α, IL-1β, IL-6, IL-12p40↓	[81]

around the world have developed several approaches to defend against the virus. Pharmacologists found that favipiravir [89] and Liahua Qingwen capsule [90] could be used to treat the COVID-19. Other studies have explored the use of ginseng on treating or preventing COVID-19 [91].

Ginseng is one of the ancient herbs in the world, as it has been used as medicine or a food ingredient for over 4000 years. However, with ongoing research, novel compounds of ginseng continue to be identified and isolated. In addition, both former and fresh compositions exhibited the infinite potentials in pharmacology, such as anti-inflammation, immunoregulatory, and anti-cancer activities. The saponins of ginseng are called ginsenosides, which exhibit many functions. Ginsenosides are classified into least four types according to their backbones. In this review, we mainly focused the immunomodulatory roles of ginsenosides *in vitro* and *in vivo*. It is worth noting that some ginsenosides are versatile. Many ginseng-derived saponins have both immunostimulatory and immunosuppressive functions, such as Rg1 in PPT-type

ginsenosides as well as Rg3 and compound K in PPD-type ginsenosides. *In vitro*, Rg1 can stimulate innate immunity on macrophages induced by LPS and enhance the Th2 immune response through PI3K/AKT and mTOR signaling pathways. However, Rg1 down-regulates Th1 immunity by suppressing the NF-κB pathway. *In vivo*, Rg1 acts as an adjuvant in many vaccines like HBsAg, eSAG1 antigen or the PRRSV vaccine. In this case, Rg1 can promote the immune responses through both Th1 and Th2. However, the mechanisms *in vivo* are extremely complex. Rg1 was also used to treat CLP-induced sepsis mice or AIA rats through relieving Th1 and Th2 immunities. Rg1 even decreased the Th1 response in type 2 RPPSV-induced piglets. Rg3 and CK showed similar properties as Rg1. In addition, CK is applied to treat transplant rejection including cardiac, islet and skin transplantation. All these studies proved that ginsenosides perform different immune responses according to the chemicals or pathogens. COVID-19 impairs innate immunity and causes pneumonia. Ginseng has been proven to have anti-inflammation and anti-bacteria or -virus effects and boost human immunity. Some researchers investigated whether ginseng could alleviate respiration disease or co-infection caused by COVID-19 [92]. Park et al. used PEGylated nanoparticle albumin-bound (PNAB) ginsenosides, PNAB-RG6 and PNAB-Rgx365 and showed that PNAB-steroidal ginsenosides alleviated the inflammation and cytokine storm in an animal model, as well as remarkably reduced the severe conditions of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in ICU patients [92]. Rg3 was also found to efficiently block the entry of pseudovirus [93].

The discussion of immunity usually involves inflammation. Immunity is classified into two categories: the nonspecific and specific reactions. The nonspecific reaction, which is called innate immunity, includes barriers or eliminators that clear the invader without specificity. The specific reaction, named adaptive immunity, removes the pathogens through a precisely targeted approach. Inflammation serves as an alarm to indicate the infection [94,95]. Although some inflammation is not detrimental, exploring whether something can boost immunity without inflammation is important. Several immunostimulants were discovered and applied into clinical trials. For example, bropirimine is an immunostimulant that was clinically used to treat the transitional bladder [96]. However, bropirimine can easily induce headache, fever, and vomiting. In some conditions of transplantation or cancer, immunosuppressants, like corticosteroids, are required. However, corticosteroids also have some side effects, such as hoarse voice and agitation [97]. Therefore, ginseng has attracted more and more attention because of its mild and tonic properties. The immunomodulatory functions of ginsenoside, the major component of ginseng, are gradually becoming more well understood. However, although some papers reported that ginsenosides have immunostimulatory and immunosuppressive functions, the mechanisms of each ginsenoside remain unclear. Numerous papers showed that ginsenosides can trigger the Th1 and Th2 immune responses but did not conduct further investigation on the underlying mechanism. On the other hand, no clear mechanism of ginsenosides in human immune system is also a big possibility for investigators because the immunological studies on ginsenosides are vast uncultivated lands. Korea and China are the top two countries in ginseng production [98]. Further investigation into the mechanisms of ginsenosides in immunology will bring tremendous benefits in not only improving public health but also boosting individual immunity.

Data availability statement

Datasets related to this article can be found at https://www.ncbi.nlm.nih.gov/pubmed, hosted at the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM).

Declaration of competing interest

The authors declare that no conflicts of interest exist.

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