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REVIEW

Astragalus polysaccharide: a review of its immunomodulatory effect

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Abstract The *Astragalus* polysaccharide is an important bioactive component derived from the dry root of *Astragalus membranaceus*. This review aims to provide a comprehensive overview of the research progress on the immunomodulatory effect of *Astragalus* polysaccharide and provide valuable reference information. We review the immunomodulatory effect of *Astragalus* polysaccharide on central and peripheral immune organs, including bone marrow, thymus, lymph nodes, spleen, and mucosal tissues. Furthermore, the immunomodulatory effect of *Astragalus* polysaccharide on a variety of immune cells is summarized. Studies have shown that *Astragalus* polysaccharide can promote the activities of macrophages, natural killer cells, dendritic cells, T lymphocytes, B lymphocytes and microglia and induce the expression of a variety of cytokines and chemokines. The immunomodulatory effect of *Astragalus* polysaccharide makes it promising for the treatment of many diseases, including cancer, infection, type 1 diabetes, asthma, and autoimmune disease. Among them, the anticancer effect is the most prominent. In short, *Astragalus* polysaccharide is a valuable immunomodulatory medicine, but further high-quality studies are warranted to corroborate its clinical efficacy.

Keywords *Astragalus* polysaccharide · Immune regulation · Immune organs · Immune cells · Anticancer

Introduction

Astragalus is a plant from the legume family, known as "Huangqi" in China. According to the *Chinese Pharmacopoeia*, the medicinal source of *Astragalus* is the dried root of *Astragalus membranaceus* (Fisch.) Bge.*var.mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge. (Zhang et al. 2021). In this regard, Fu et al. reported that *Astragalus membranceus* (Fisch.) Bge. and *Astragalus membranceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao are two varieties of the same species (Fu et al. 2014). Prior in vivo and in vitro studies have demonstrated that *Astragalus* possesses multiple biological functions, such as immunomodulation, antioxidant, anti-inflammation and antitumor properties and thus widely used for the treatment of cardiovascular diseases, diabetes mellitus, cancer, respiratory diseases, nervous system diseases and other diseases (Song et al. 2011, 2013; Qin et al. 2012; Jung et al. 2016). *Astragalus* polysaccharide is an important natural active component derived from *Astragalus* (Jin et al. 2014). An increasing body of evidence from pharmacological studies has shown that *Astragalus* polysaccharide has a variety of biological activities such as regulating blood glucose and blood lipids, anticancer, anti-aging, and immune regulation, amongst which the immunomodulatory effect is the most important (Chen et al. 2020; Zheng et al. 2020).

Therefore, this review systematically reviewed the evidence on the immunomodulatory effect of *Astragalus* polysaccharides. It has been established that *Astragalus* polysaccharide can regulate the activities of immune organs (bone marrow, thymus, lymph node, spleen and mucosa-associated

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lymphoid tissue) and immune cells (macrophage, natural killer cell, dendritic cell, T lymphocyte, B lymphocyte and microglia) and the release of immune active substances (such as IL-2 (interleukin-2), IL-6, TNF-α (tumor necrosis factor-α), IFN-γ (interferon-γ), IgA (immunoglobulin A), IgG, and IgM) (Xie et al. 2016; Farag and Alagawany 2018; Wang et al. 2019; Wan et al. 2022). Then, we systematically reviewed the therapeutic effect of *Astragalus* polysaccharides on immune-related diseases. *Astragalus* polysaccharide can be used for anticancer, anti-infection and as vaccine adjuvants by enhancing the activity of immune cells and the release of immune active substances. Moreover, *Astragalus* polysaccharide is indicated for autoimmune diseases, including type 1 diabetes, asthma and inflammatory demyelinating disease, given its ability to inhibit an overactivated immune system (Zhang et al. 2019b; Kong et al. 2021). In addition, the immunomodulatory effect of ASPC (*Astragalus* polysaccharide component) and pure polysaccharide (by further purification and separation) are distinguished to broaden current understanding and trigger further interest in exploring the relationship between the structure and immunomodulatory activity of *Astragalus* polysaccharide.

Pharmacological activities on immune organs

The immune organs represent an important part of the immune system and can be divided into central and peripheral immune organs according to their functions. The central immune organs of humans or other mammals include the bone marrow and thymus (Ganea et al. 2015). Peripheral immune organs include lymph nodes, spleen and mucosa-associated lymphoid tissues. They are the sites where mature lymphocytes colonize and the main site for lymphocytes to produce immune responses (Scheffer and Latini 2020).

Pharmacological activities on the bone marrow

The bone marrow can produce pluripotent hematopoietic stem cells and is the birthplace of various blood cells and immune cells (Zhao et al. 2012). Current evidence suggests that *Astragalus* polysaccharide has a protective effect on bone marrow stem cells. ASPC (50 μg/ml) could protect bone marrow mesenchymal stem cells from radiation-induced apoptosis by inhibiting the production of reactive oxygen species, upregulating the proteins B-cell lymphoma-2 (Bcl-2) and B-cell lymphoma extra-large (Bcl-xl), and downregulating the proteins Bcl-2-associated X (Bax) and Bcl-2 homologous killer (Bak) (Zhang et al. 2020b). Moreover, ASPC (40–400 μg/ml) could protect bone marrow mesenchymal stem cells from formaldehyde-induced cytotoxicity and genotoxicity by upregulating the expression of xeroderma pigmentosum group A, xeroderma pigmentosum group C, excision repair cross-complementation group 1, replication protein A1, and replication protein A2 (She et al. 2021). Exploring the immunomodulatory effect of *Astragalus* polysaccharides on immune organs is of great significance for an in-depth understanding of the regulation of immune cells and immune factors by *Astragalus* polysaccharides (Jia et al. 2019). In cyclophosphamide-induced immunosuppressive rats, ASPC (100 mg/kg) improved the chemotactic capacity of polymorphonuclear leukocytes among mature bone marrow granulocytes and peripheral blood neutrophils by regulating the L-selectin signaling pathway, and upregulating the expression of P-selectin glycoprotein ligand-1, CD11b (cluster of differentiation 11b)/CD18, TNF-α and IL-8 (Zhang et al. 2015). In radiation-induced bone marrow immunosuppressive mice, ASPC (50–500 mg/kg) promoted the colony formation of megakaryocytes, granulocyte monocytes, and erythroid cells and inhibited apoptosis of megakaryocytic cells by inhibiting the activation of the mitochondrial apoptotic pathway (Li et al. 2021a). In addition, some pure polysaccharides obtained by further purification and separation can stimulate immune activity in the immunosuppressive bone marrow. It has been established that the glucose, galactose, arabinose, rhamnose, and the galacturonic acid ratio is 1.5:1:5.4:0.08:0.1 in *Astragalus* polysaccharide-I (APS-I) (molecular weight above 500 kDa) and 9:1:1.4:0.04:0.001 in APS-II (*Astragalus* polysaccharide-II) (molecular weight 10 kDa) (Li et al. 2020d). APS-I and APS-II (5–20 mg/kg) could increase the levels of white blood cells, lymphocytes, monocytes and neutrophils, and the expression of IL-2, IL-6, IgG, and granulocyte-macrophage colony-stimulating factor (GM-CSF), and decrease $CD4^+/CD8^+$ level in cyclophosphamide-induced immunosuppressive mice (Li et al. 2020d). The pure polysaccharide *Radix Astragali* polysaccharide (RAP) consists of rhamnose, arabinose, glucose, galactose and galacturonic acid with a molar ratio of 0.03:1.00:0.27:0.36:0.30, and a molecular weight of 1334 kDa. The backbone consists of 1,2,4-linked Rha*p*, α-1,4-linked Glc*p*, α-1,4-linked GalA*p*6Me, and β-1,3,6-linked Gal*p* (Yin et al. 2012). RAP (150 mg/kg) has been shown to protect mice hematopoietic stem cells from cyclophosphamide-induced myelosuppression by inhibiting bone marrow cell apoptosis, promoting bone marrow cell proliferation, and increasing the number of hematopoietic stem cells, $CD34^+$ cells, lineage-negative cells, $Lin^-c\text{-}Kit^+$ cells, and $Lin^-Sca1^+c\text{-}Kit^+$ cells (Bao et al. 2021).

Pharmacological activities on the thymus

The thymus is another important central immune organ, which is the site of T lymphocyte development, differentiation and maturation (Sakaguchi et al. 2011). Current research shows that *Astragalus* polysaccharides can promote proliferation and improve drug-induced apoptosis in

thymocytes. In cyclophosphamide-induced immunosuppressive mice, ASPC (50–80 mg/kg) enhanced the thymus index and serum levels of immunoglobulins (IgA, IgG, and IgM) and inhibited the overproduction of IL-2 (Meng et al. 2017). In doxorubicin hydrochloride-induced immunosuppressive lung cancer mice, the pure polysaccharide APS-III (*Astragalus* polysaccharide-III), with a backbone consisting of Glc(1–4), Xyl(1–2), Gal(1–4), and GalA(1–3), (15%) also significantly increased the thymus index. Further research showed that it might be related to the inhibition of drug-induced thymocytes apoptosis by suppressing the activation of the mitochondrial apoptotic pathway, upregulating the proteins Bcl-2 and Bcl-xl, and downregulating the proteins Bax and Bak (Zhou et al. 2018). The pure polysaccharide AX-I-3b [*Astragalus radix* (*radix*) polysaccharide-I-3b] consists of arabinose, xylose, and glucose with a molar ratio of 10.4:79.3:1.1, and a molecular weight of 7.87 kDa (Li et al. 2019a). AX-I-3b (50–200 mg/kg) also improved cisplatin-induced decrease in thymus organ index and increased the ratio of $CD4^+$ T cells to $CD8^+$ T cells and the expression of IL-2, IL-6 and TNF-α in lung cancer mice (Li et al. 2019a).

Pharmacological activities on the spleen

The spleen is the largest peripheral immune organ, which can synthesize and secrete complement, interferon and other substances and trigger immune responses to blood-derived antigens (Bronte and Pittet 2013). Growing evidence shows that *Astragalus* polysaccharide can promote the proliferation of spleen cells and the release of biologically active substances. In this respect, ASPC (1–500 μg/ml) could enhance in vitro mice splenic lymphocytes proliferation and increase the T-cell $CD4^+/CD8^+$ ratio (Xu et al. 2019). Polysaccharide-rich *Astragalus* extract (1 g/kg) promoted splenocytes proliferation and increased the levels of peripheral white blood cells, splenic lymphocyte subset, IgG and IgM in cyclophosphamide-induced immunosuppressive mice (Li et al. 2021d). In ovalbumin subcutaneously immunized mice, ASPC (1–4 mg/ml) promoted the proliferation of splenocytes, the secretion of IFN-γ and IL-6 and the specific immunoglobulins antibody response (IgG, IgG1 and IgG2a) (Fan et al. 2013). In carboplatin-induced immunosuppression in B16 tumor-bearing mice, ASPC (10 g/kg) alleviated immune suppression by inducing the proliferation of spleen cells and secretion of immune regulatory factors, such as IL-1β, IL-6 and TNF-α (Wu et al. 2016). Paternal dietary ASPC (10 g/kg) transgenerationally could induce an endotoxin tolerance-like immune response in the spleen of broiler chickens by increasing serum IFN-α and IFN-β levels by activating the TLR4 (toll-like receptor 4) signaling pathway in jejunal mucosa (Li et al. 2018b).

Pharmacological activities on mucosal tissue

Mucosal-associated lymphoid tissue, also called the mucosal immune system, mainly responds to microorganisms that enter through the mucosal surface (Tesher et al. 2019). Yupingfeng polysaccharide fraction (ASPC as the main ingredient, 10 ml/kg), could improve rabbits intestinal barrier integrity and functionality and increase the levels of IL-1, IL-2, IL-4, IL-6, IL-10, IL-12, TNF-α, and IFN-γ by activating TLR2 and TLR4 signaling pathways (Sun et al. 2016). The Bu-Zhong-Yi-Qi-Tang polysaccharide fraction (ASPC as the main ingredient, 45 mg/kg) also increased mucosal immune activity in mice, enhanced the activity of T lymphocytes in Peyer's patches and induced the production of IL-2, IL-4, IL-5 and IFN-γ (Liu et al. 2019b). In ovo injection of ASPC (1–4 mg/kg) was found to enhance the intestinal mucosal immunity of broiler chickens by increasing the levels of IL-2, IL-4, IFN-γ, and TLR-4 and the number of IgA^+ cells in the early stage after hatching (Yang et al. 2021). ASPC (0.6 mg/ml) could regulate the intestinal mucosal immune function of reovirus-infected muscovy ducklings by increasing the ileal secretory IgA and duodenal cytokine levels of IL-4, IL-6, IL-15, TNF-α, and INF-γ (Liao et al. 2021). For rats vaccinated with recombination urease subunit B, using ASPC (1.25–10 mg/ml) as an adjuvant could increase the levels of ovalbumin-specific IgG in serum and secretory IgA in saliva, vaginal wash and intestinal lavage fluid by activating the TLR2 signaling pathway and resulting in mixed specific T helper 1 (Th1) cells and Th17 cells immune response (Liu et al. 2019a). The pure polysaccharide *Astragalus* polysaccharide (APS) consists of glucose, arabinose, xylose and mannose with a molar ratio 95.0:2.9:0.7:0.7:0.6, and a molecular weight of 17.39 kDa. APS (50 mg/kg) could activate the dendritic cells, cytotoxic T lymphocytes, and natural killer cells of the mesenteric lymph nodes, thereby promoting the inhibitory effect of programmed death ligand-1 (PD-L1) antibody on the growth of metastatic lung melanoma in mice (Hwang et al. 2021). The pure polysaccharide AMA-1-b-PS2 (Arabino-3,6-galactan) consists of arabinose, fucose, galactose, glucose, mannose, rhamnose, xylose, galacturonic acid, glucuronic acid and glucose acid with a molar ratio of 12.8:4.5:25.6:23.6:24.8:5.1:0.7:1.5:1.5:1.4. The backbone is composed of β-D-(1→3) linked galactans. In mice small intestines, AMA-1-b-PS2 (10–100 μg/ml) could contribute to immunomodulation of Peyer's patch cells by activating the T cell response and promoting the production of IL-2, IL-6 and TNF-α (Lim et al. 2016).

In short, current evidence suggests that *Astragalus* polysaccharide can stimulate the immune function of the bone marrow, thymus, spleen and mucosal immune system and further activate a variety of immune cells to produce immune factors, including macrophages, glial cells, natural killer cells, dendritic cells, and T lymphocytes.

Pharmacological activities on immune cells

Pharmacological activities on macrophages

It is widely acknowledged that monocytes leave the blood vessels and distribute to various tissues, becoming macrophages. Macrophages are not only the main effector cells of innate immunity but also play an important role in the process of the adaptive immune response (Poupot et al. 2018). Cell research has shown that ASPC (6.25–100 μg/ml) could increase the expression of IL-1β, IL-6, IL-8, TNF-α, IFN-γ and iNOS (inducible nitric oxide synthase) in primary head kidney macrophages (Zhang et al. 2020a). Moreover, ASPC (12.5–100 μg/ml) could stimulate the activity of RAW264.7 macrophages and increase the production of NO, IL-1β, IL-6 and TNF-α (Zhao et al. 2011). Studies have shown that this stimulation effect was related to the activation of.

TLR4/MyD88 (myeloid differentiation factor 88) signaling pathway (Zhou et al. 2017; Li et al. 2019d). In addition, studies have also shown that this promotion effect was related to the activation of NF-κB (nuclear factor κ-B) and MAPK (mitogen-activated protein kinase) signaling pathways (Lee and Jeon 2005; Zhu et al. 2018; Feng et al. 2020,). Wang et al. found that secondary messengers were involved in the immune regulation of RAW 264.7 macrophages by ASPC (25 μg/ml), including increasing the levels of NO, diglycerides, inositol 1,4,5-triphosphate, and cyclic adenosine monophosphate (Wang et al. 2017). In addition, ASPC could improve immune stress in macrophages. In this respect, ASPC (10–30 μg/ml) inhibited the expression of IL-1β, IL-6 and TNF-α in ochratoxin A-induced porcine alveolar macrophages (Liu et al. 2018b). In LPS-induced RAW264.7 macrophages, ASPC (10–300 μg/ml) also decreased the expression of NO, IFN-γ, IL-1β, IL-22 and TNF-α (Liao et al. 2018). In vivo research further confirmed the immunomodulatory effect of ASPC on macrophages. In *Brucella*-infected mice, ASPC (50–200 μg/ml) promoted the activation of macrophages and the production of proinflammatory cytokines, including TNF-α, IL-12 and IFN-γ (Shi et al. 2019). ASPC (200 mg/kg) promoted defective alveolar macrophage phagocytosis and decreased IL-6, IL-8, and TNF-α levels in bronchoalveolar lavage fluid and serum in chronic obstructive pulmonary disease mice (Chu et al. 2016).

In addition, scholars have explored the immunomodulatory effect of several pure polysaccharides on macrophages. The pure polysaccharide AP (*Astragalus* polysaccharide), an α-D-glucan (300 mg/kg), promoted macrophage phagocytosis and the secretion of immune-related cytokines such as GM-CSF, TNF-α, IL-4 and IL-10 by activating the TLR4 signaling pathway in normal mice (Moreno-Mendieta et al. 2017; Peng et al. 2019). The pure polysaccharide APSII (*Astragalus* polysaccharide II) consists of xylose, glucuronic, arabinose, rhamnose, mannose, and galactose with a molar ratio of 9.22:77.89:1:5.18:4.54:2.17, and a molecular weight of 11.4 kDa (Lv et al. 2016). APSII (10–80 μg/ml) promoted the maturation of RAW264.7 macrophages by increasing the expression of MHC II (major histocompatibility complex II), CD40, CD80 and CD86 (Lv et al. 2016). The pure polysaccharide AMP (*Astragalus membranaceus* polysaccharide) consists of glucose, arabinose, and galactose with a molar ratio of 91.0:6.2:2.8 and a molecular weight of 804 kDa (Li et al. 2020a). AMP (10–100 μg/ml) has been reported to stimulate RAW264.7 macrophages to produce NO by activating the NF-κB and MAPK signaling pathways (Li et al. 2020a). The pure polysaccharide RAP (30–300 μg/ml) could also promote the production of NO, TNF-α and IL-6 in RAW264.7 macrophages by activating the NF-κB and MAPK signaling pathways (Wei et al. 2016; Li et al. 2017, 2018c). In addition, RAP (30–300 μmol/L) could induce mice macrophages polarization to the M1 phenotype by inducing higher expression of M1 marker genes, including iNOS, IL-6, TNF-α and CXCL10 (chemokine (C-X-C motif) ligand 10) (Wei et al. 2019). In addition, RAP (10–100 μg/ml) could protect RAW264.7 macrophages from cell cycle arrest and apoptosis induced by paclitaxel by downregulating the protein levels of phospho-histone H_2A. X, poly ADP-ribose polymerase, checkpoint kinase 1, p53 and p21, and upregulating the levels of Bax and myeloid cell leukemia-1 (Bao et al. 2018). In short, *Astragalus* polysaccharide can promote the activity of macrophages by activating the NF-κB and MAPK signaling pathways and induce the expression of a variety of cytokines.

Pharmacological activities on T and B lymphocytes

T and B lymphocytes are two important lymphocytes in the body. T lymphocytes can promote the proliferation and activation of other immune cells through the production of cytokines and directly kill target cells. The basic function of B lymphocytes is to produce antibodies, present antigens and secrete cytokines (Locatelli et al. 2013). In vivo studies showed that ASPC (8 mg/kg) improved the immunity of cyclophosphamide-induced immunosuppressive mice by promoting proliferation of T lymphocytes and B lymphocytes, and inducing the production of a variety of cytokines, including IgA, IgG, IgM, IL-6, IL-2, IFN-γ, complement 3, complement 4 and TNF-α (Yu et al. 2016; Meng et al. 2017). For mice vaccinated with HBV (hepatitis B virus)-DNA vaccine, ASPC (500 μg/mouse) as an adjuvant promoted the proliferation and the activity of T lymphocytes, induced $CD4^+$ T cells to produce IL-4, IL-2 and IFN-γ, enhanced the expression of IFN-γ in $CD8^+$ T cells, and reduced the frequency of regulatory T cells (Du et al. 2012). In spleen deficiency syndrome mice (induced by a high-fat, low-protein diet and exhausting swimming), ASPC (300–1200 mg/kg)

increased the percentages of $CD3^+$ and $CD3^+CD4^+$ T cells and the ratio of $CD3^+CD4^+/CD3^+CD8^+$, and reduced the expression of IL-6, IL-10 and TNF-α (Kang and Yu 2018; Zhao et al. 2019). $CD4^+CD25^+$ Treg cell is a kind of T lymphocyte with immunosuppressive effect and can inhibit the activation and proliferation of T lymphocytes (Haufe et al. 2011). In the microenvironment of human hepatocellular carcinoma, ASPC (10–200 μg/ml) could inhibit the growth, proliferation and migration of $CD4^+CD25^+$ Treg cells by inhibiting the activation of chemokine (C-X-C motif) receptor 4 (CXCR4)/CXCL12 signaling pathway, blocking chemokine stromal-derived factor-1 and its receptor and restoring the imbalance of cytokines (increasing IFN-γ expression and decreasing IL-4 and IL-10 expression) (Li et al. 2012). The pure polysaccharide *Astragalus* polysaccharide-IV (APS-IV) is an α-1,4-D-glucan with a molecular weight of 20.7 kDa. The pure polysaccharide *Astragalus* polysaccharide-V (APS-V) consists only of arabinose, and the molecular weight was 40.1 kDa. The pure polysaccharide *Astragalus* polysaccharide-VI (APS-VI) consists of rhamnose, glucose, galactose and arabinose with a molar ratio of 1:10.76:6.55:12, and a molecular weight of 15.3 kDa (Niu et al. 2011; Jiang et al. 2016). In vitro research has shown that APS-IV (100–250 μg/ml), APS-V (6.25–800 μg/ml) and APS-VI (6.25–800 μg/ml) could effectively stimulate the proliferation of mouse T lymphocytes and B lymphocytes (Niu et al. 2011; Jiang et al. 2016). In short, *Astragalus* polysaccharides can improve immune suppression and enhance tumor immunity by promoting the proliferation of T lymphocytes and B lymphocytes, increasing the secretion of related cytokines and inhibiting the activity of regulatory T cells.

Pharmacological activities on natural killer cells

The natural killer cell is a kind of lymphocyte from bone marrow lymphoid cells distributed in peripheral blood and the spleen (Huntington et al. 2020). Given that the cytotoxic effect of natural killer cells does not require antigen pre-sensitization and there is no MHC restriction, natural killer cells play an important role in antitumor immunity (Battella et al. 2016). In vitro research has shown that the pure polysaccharide AMP (10–100 μg/ml) could activate and promote the proliferation of mouse natural killer cells by up-regulating the expression of IFN-γ, TNF-α, granzyme-B, and NKp44 (a natural cytotoxicity receptor) (Li et al. 2020a). Mu et al. further explored the mechanism of *Astragalus* polysaccharide in activating natural killer cells. In H22 tumor-bearing mice, ASPC (10–100 mg/kg) upregulated the expression of major histocompatibility complex class I chain-related molecule A (MICA) and MICB on the tumor cell surface which represent the major ligands of activating receptor NKG2D on natural killer cells. The binding of MICA/B and NKG2D led to natural killer cell activation by increasing the phosphorylated extracellular signal-regulated kinase level. Activated natural killer cells released IFN-γ, granzyme-B and perforin and promoted the clearance of cancer cells (Mu et al. 2019). In addition, ASPC (10 g/kg) ameliorated natural killer cell-mediated cytotoxicity in breeder cock testes by reducing levels of IFN-γ, perforin, DNA-binding protein (high mobility group-2 (HMG-2), and lysin (Wu et al. 2017). In conclusion, experimental studies have confirmed that *Astragalus* polysaccharide can regulate the activity of natural killer cells and the expression of immune factors such as IFN-γ, TNF-α, granzyme-B and perforin.

Pharmacological activities on dendritic cells

Dendritic cells differentiate from myeloid stem cells and lymphoid stem cells and are widely distributed in various organs except for brain tissue (Shang et al. 2017). Research has shown that *Astragalus* polysaccharide can promote the maturation of dendritic cells. ASPC (500 μg/mouse) as an adjuvant could stimulate the maturation of dendritic cells and upregulate the expression of MHC I/II, CD40, CD80 and CD86 in mice vaccinated with the HBV-DNA vaccine (Du et al. 2012). The pure polysaccharide APSII (1.67–45 μg/ml) could also promote the maturation of dendritic cells by inducing the production of NO and increasing the expression of CD40, CD80, CD86 and MHC-II (Zhu et al. 2016). In the normal mice, the pure polysaccharide AMP (100–500 mg/kg) increased the levels of CD40, CD80, CD86, MHC I and MHC II in splenic dendritic cells and their subsets and promoted the production of proinflammatory cytokines such as IL-6, IL-12p70 and TNF-α (Lim et al. 2021). Since dendritic cells are the most powerful antigen-presenting cells in the body, their activity is essential for developing, differentiating, and activating T and B lymphocytes (Kambayashi and Laufer 2014). It has been reported that ASPC (50–200 μm/ml) induced the differentiation of splenic dendritic cells to IL-12-producing $CD11c^{high}$ $CD45RB^{low}$ dendritic cells and further induced activation of T lymphocytes with the transformation of T helper 2 cells to T helper 1 cells (Liu et al. 2011). ASPC (10 mg/kg) induced phenotypic maturation of dendritic cells by upregulating the expression of MHC-II, CD80 and CD86, which in turn induced cytotoxic T lymphocyte activation and immune factor TNF-α, IFN-γ, IL-4, IL-10, and IgG1 production in 4T1 tumor-bearing mice (Xiong et al. 2020). In non-small cell lung cancer-bearing mice, ASPC (3 mg/kg) could promote the functional maturation of dendritic cells and increase the population of $CD80^+$, $CD103^+$, and $CD86^+$ functionally matured dendritic cells, thereby enhancing the anticancer immune response mediated by T lymphocytes (Bamodu et al. 2019). In conclusion, upregulation of the expression of IL-6, IL-12p70, TNF-α, CD40, CD80, CD86 and MHC I/II by *Astragalus* polysaccharide indicates that it can stimulate the activity of

dendritic cells and thus promote the activation of T and B lymphocytes.

Pharmacological activities on microglia

Microglia function as a sentinel for innate immunity in the central nervous system. Under different cell microenvironment conditions, microglia can differentiate into two phenotypes: the M1 type with a proinflammatory effect and the M2 type with an anti-inflammatory effect (Saijo et al. 2013). ASPC (200 μg/ml) could inhibit LPS-induced microglial activation and the expression of various proinflammatory factors, including prostaglandin E2, iNOS, cyclooxygenase-2, IL-1β and TNF-α by inhibiting the NF-κB and AKT (protein kinase B) signaling pathways (Luo et al. 2015). Jia et al. found that ASPC (22.5–45 mg/kg) reversed the polarization of rat microglia M1/M2, decreased the matrix metalloproteinaseprotein-9 expression, and maintained the integrity of blood brain barrier in the middle cerebral artery occlusion rats by inhibiting the expression of P2×7R (purinergic receptor) and promoting the degradation of ATP in microglia (2022). In addition, Liu et al. found that miR-155 mediated the polarization of microglia M1/M2 phenotype. ASPC (0.4–0.8 mg/ml) regulated the polarization of microglia from the M1 to M2 phenotype by inhibiting miR-155 expression, reducing the secretion of inflammatory factors IL-1α and TNF-α, and inhibiting the activation of neurotoxic astrocytes in experimental autoimmune encephalomyelitis mice (Liu et al. 2021). In mice treated with a high-fat diet and low-dose streptozotocin, ASPC (500 mg/kg) reduced metabolic stress-induced astrogliosis and microglial activation in brain plaques by diminishing the immunoreactivity of the ionized calcium-binding adaptor molecule-1 (Huang et al. 2017). In conclusion, *Astragalus* polysaccharide can inhibit the activation of microglia and inhibit the inflammatory response of the nervous system.

Pharmacological activities on immunological diseases

Pharmacological activities on cancer

The body's immune response to tumors involves innate immunity and adaptive immunity. For cancer cells with weak immunogenicity, innate immunity plays a major role, and the main participating cells include macrophages, natural killer cells and γδ T cells (Sun et al. 2018). It has been shown that *Astragalus* polysaccharides can boost the body's immune response to cancer by activating macrophages, dendritic cells, and natural killer cells by promoting their proliferation and differentiation, increasing the secretion of cytokines such as IL-2, TNF-α and IFN-γ, and alleviating the state of immune suppression (Balakrishnan et al. 2021; Li et al. 2021c). Macrophages are not only used as antigen-presenting cells during tumor immunity but also as effector cells that kill cancer cells (Van den Bossche et al. 2017). Research has shown that ASPC (0.1–100 mg/ml) could induce MCF-7 human breast cancer cell apoptosis by activating RAW 246.7 macrophages and promoting the expression of NO and TNF-α (Li et al. 2018a, 2019d). In 4T1 tumor-bearing mice, ASPC (50–1000 μg/ml) enhanced the proliferation of spleen lymphocytes and phagocytosis of peritoneal macrophages and upregulated the expression of IL-2, TNF-α and IFN-γ in the peripheral blood (Li et al. 2020e). In Ehrlich ascites carcinoma mice models, ASPC (500 mg/kg) also promoted the production of TNF-α, IL-1β, and IL-6 by activating RAW 264.7 macrophages, thereby inducing apoptosis of cancer cells. The qRT-PCR and Western blotting indicated that it was related to the activation of the MyD88-dependent signaling pathway mediated by TLR4 (Zhou et al. 2017; Li et al. 2020f). Natural killer cells and γδ T cells are effector cells that play an important role in early antitumor immunity and represent the body's first line of defense against tumors (Johnsrud et al. 2020). In S180 sarcoma-bearing mice, ASPC (150–300 mg/kg) induced apoptosis of cancer cells by promoting the proliferation of γδ T cells and inducing the expression of IFN-γ, Fas ligand and granzyme B (Sun et al. 2014). In addition to enhancing the body's immune response to cancer, the immunomodulatory effect of ASPC is reflected in its ability to improve cancer-related inflammation. Clinical research has found that ASPC (250–500 mg/day) could reduce the levels of IL-1β, IL-6, IL-12, GM-CSF, transforming growth factor β1 (TGF-β1) and IFN-γ and improve complications of cancer including pain, nausea, vomiting, and fatigue in cancer patients (Huang et al. 2019). The pure polysaccharide cAMPs-1 A (cold-water-soluble *Astragalus* polysaccharide-1 A) consists of fucose, arabinose, galactose, glucose, xylose with a molar ratio of 0.01:0.06:0.20:1.00:0.06, and a molecular weight of 12.3 kDa (Liu et al. 2018a). The pure polysaccharide ASP (alcohol-soluble *Astragalus* polysaccharide) consists of arabinose, galactose, glucose and mannose with a molar ratio of 1.00:0.98:3.01:1.52, and a molecular weight of 2.1 kDa (Yu et al. 2018). Studies have shown that cAMPs-1 A (300 mg/kg) and ASP (100–300 mg/kg) could induce tumor cell apoptosis by promoting the activities of natural killer cells, macrophages and T lymphocytes and the expression of TNF-α, IL-2 and IFN-γ in B16 or H22 tumor-bearing mice (Liu et al. 2018a; Yu et al. 2018). This finding confirms that the tumor immunity induced by *Astragalus* polysaccharide involves a variety of immune cells.

T lymphocyte is another important cell of tumor immunity. Tumor antigen mainly induces two types of T lymphocyte subpopulations in the body to respond, including $CD4^+$ T cell restricted by MHC II and $CD8^+$ T cell restricted by

MHC I (Rivoltini et al. 2002). In H22 tumor-bearing mice, ASPC (50–400 mg/kg) induced apoptosis and inhibited the growth of tumor cells by increasing the spleen and thymus indexes and promoting T lymphocytes to produce IL-2, IL-6 and TNF-α (Lai et al. 2017). In S180 tumor-bearing mice, ASPC (150–300 mg/kg) induced the apoptosis of tumor cells by upregulating the proportion of $CD3^+$, $CD4^+$, $CD8^+$ T cells and $CD19^+$ B cells in the thymus, peripheral blood and spleen (Yu et al. 2021). In mouse mammary carcinoma 4T1 cells, ASPC (100–200 μg/ml) enhanced the expression of CD40, CD80 and CD86 markers in dendritic cells, immunomodulatory cytokines and chemokines including TNF-α, IL-6, CCL1 (chemokine (C-C motif) ligand 1), CCL3, CXCL1, CXCL2, CXCL10 and the proliferation of $CD4^+$ T cells and $CD8^+$ T cells (Chang et al. 2015; Pang et al. 2019a, b). In Lewis tumor-bearing mice, the pure polysaccharide AX-I-3b (50–200 mg/kg) improved the immunosuppression caused by cisplatin by increasing the ratio of $CD4^+$ T cells to $CD8^+$ T cells and the expression of IL-2, IL-6 and TNF-α (Li et al. 2019a). The pure polysaccharide AP-I (extract of *Astragalus*-I), an α-(1→4)-D-glucan with α-(1→6)-linked branches, could promote the proliferation of spleen lymphocytes and increase the levels of IL-2, IgA, IgG and IgM and natural killer cells activities in gastric cancer rats at 300 mg/kg (Li et al. 2009). In addition, ASPC (10–200 μg/ml) could inhibit the activation of $CD4^+CD25^+$ Treg cells in the microenvironment of human hepatocellular carcinoma by restoring cytokine imbalance (increasing IFN-γ expression and decreasing IL-4 and IL-10 expression) and reducing FOXp3 (forkhead box protein p3) expression, thereby eliminating the immunosuppression and promoting the apoptosis of cancer cells (Li et al. 2012).

Programmed death 1 (PD-1) is an immune checkpoint that can inhibit the function of immune cells, prevent the body from producing an effective antitumor immune response, and induce immune escape of tumor cells (Xu-Monette et al. 2018). It has been reported that ASPC (50 mg/kg) could downregulate the expression of PD-L1 on the surface of breast cancer 4T1 cells and colorectal cancer CT26 cells and block the effect of PD-L1-induced T cell exhaustion by inhibiting the AKT/mammalian target of rapamycin/ribosomal protein S6 kinase β-1 signaling pathway in tumor-bearing mice (Chang et al. 2020a, b). A study involving 53 lung cancer patients showed that ASPC (500 mg/person) could alleviate poor response and improve survival after treatment with immune checkpoint inhibitors by normalizing the neutrophil-to-lymphocyte ratio (Tsao et al. 2021). Myeloid-derived suppressor cells also play a role in immune suppression in cancer. Myeloid-derived suppressor cells are pathologically activated myeloid cells that are potent suppressors of T cells and natural killer cells (Gabrilovich 2017). In the co-culture of peripheral blood mononuclear cells with HeLa cervical cancer cells, ASPC (15–1000 μg/ml) inhibited myeloid-derived suppressor cells proliferation and the induction of Treg cells and promoted the production of TGF-β, IL-6, IFN-γ and IL-10 by peripheral blood mononuclear cells (Shokati et al. 2021). In the co-culture of bone marrow-derived mesenchymal stem cells with A549 lung cancer cells, ASPC (50 μg/ml) inhibited myeloid-derived suppressor cells proliferation and morphological changes by inhibiting the activation of the MAPK/NF-κB signaling pathway and reducing the protein expression levels of acetylated H4K5 (histone H4 lysine 5), acetylated H4K8, and acetylated H3K9 (Zhang et al. 2019a). In melanoma-bearing mice, ASPC (50–200 mg/kg) reduced the number of myeloid-derived suppressor cells and the expression of Arg-1, IL-10 and TGF-β, which increased the cytotoxic effect of $CD8^+$ T cells against tumor cells. Spearman correlation analysis showed that it was related to ASPC remodeling the gut microbiota (Ding et al. 2021; Tian et al. 2012). In addition, ASPC (10 mg/kg) could inhibit vascular endothelial growth factor (VEGF) production in 4T1 tumor-bearing mice and inhibit the proliferation and migration of cancer cells by inducing the production of single-chain fragment variable antibody 4E (scFv 4E). Molecular docking simulations revealed that the main driving force for the interaction of scFv 4E and VEGF involved the hydrophobic interactions and hydrogen bonds of Tyr108 and Tyr 109 of the complementarity-determining region H3 loop with VEGF (Lee et al. 2020).

In summary, these studies substantiate that *Astragalus* polysaccharide can promote tumor immune response by stimulating the activity of a variety of immune cells. In addition, *Astragalus* polysaccharide can inhibit tumor immune escape by inhibiting the activity of regulatory T cells and immune checkpoints.

Pharmacological activities against viral infection

ASPC (120 μg/ml) could protect mouse astrocytes from herpes simplex virus (HSV)-1 infection by increasing the expression of TNF-α and IL-6 by activating the TLR3/NF-κB signaling pathway (Shi et al. 2014). ASPC (10 μg/ml) could modulate the immune activity of porcine endothelial cells exposed to CSFV (classical swine fever virus) by increasing the levels of IFN-α, IFN-β, IL-1, IL-6, and IL-8 (Zhuge et al. 2017). In vivo studies have further shown that *Astragalus* polysaccharide could exert an antiviral effect by improving the body's immune function. Current evidence suggests that ASPC (2 g/kg) could improve the resistance of crucian carp against SVCV (spring viremia of carp virus) infection by upregulating the expression of IgM, IL-8, IL-10, IL-1β, IFN-α, IFN-γ, MyD88, TGF-β and TNF-α in the spleen, kidney, liver and intestine (Liu et al. 2022). In zebrafish infected by the SVCV, ASPC (0.01%) upregulated the levels of IL-10, tight junction protein 1b, and occludin1

and increased the expression of antiviral genes in the spleen, including IFNφ1, IFNφ2, and IFNφ3 (Li et al. 2021b). In intestinal inflammatory damage of goslings infected with parvovirus, ASPC (0.3 ml) decreased the expression of secreted IgA, IL-1β, IL-6 and TNF-α in the jejunal tissue and increased the levels of serum IgG, IgM, complement 3, complement 4, IFN-γ (Luo et al. 2021). ASPC (0.2 g/kg) enhanced immune response in shrimp attacked by white spot syndrome virus by promoting hemocyte proliferation and phagocytic activity and increasing the activities of phenoloxidase, total superoxide dismutase and lysozyme (Chang et al. 2018).

In addition, *Astragalus* polysaccharide has been reported as an adjuvant for viral vaccine by activating macrophages, natural killer cells, T and B lymphocytes, and the complement system, promoting the secretion of immune factors, and so on (Wang et al. 2021). ASPC used as a vaccine carrier enhanced the immune response in Swiss albino mice vaccinated with seasonal influenza A (H3N2) vaccine by inducing Th1/Th2 balance and the production of IL-17 and IgG1 antibody (Yakuboğulları et al. 2019). ASPC as a vaccine delivery system increased the immune response to the newcastle disease vaccine in zebrafish by enhancing the production of neutralizing antibodies and the minor augmentation of IFN-α and IL-2 levels (Yakubogullari et al. 2021). For mice vaccinated with HBV-DNA vaccine, ASPC (500 μg/mouse) as an adjuvant stimulated the maturation of dendritic cells, upregulated the expression of MHC I/II, CD40, CD80 and CD86, induced $CD4^+$ T cells to produce IL-4, IL-2 and IFN-γ, enhanced the expression of IFN-γ in $CD8^+$ T cells, and reduced the frequency of regulatory T cells (Du et al. 2012). In ovo administration of live newcastle disease vaccine with ASPC (0.5 ml) as an adjuvant could stimulate stronger humoral and cellular responses in newly hatched chicks by increasing the concentrations of IFN-γ, IL-2, IL-4 and IL-6, promoting lymphocyte proliferative capability as well as improving the frequencies of $CD4^+$ and $CD8^+$ T cells (Shan et al. 2019; Xue et al. 2020). ASPC (10–100 mg/kg) could be used as an adjuvant for the avian infectious bronchitis virus vaccine and promote lymphocyte proliferation and the expression of IL-1β, IL-2, IL-8, and TNF-α in chicken (Zhang et al. 2017). These findings indicate that *Astragalus* polysaccharide may be an effective adjuvant to optimize the response to viral vaccines.

Pharmacological activities against bacterial infection

Studies have shown that *Astragalus* polysaccharide could exert an antibacterial effect by improving the body's immune function. The use of ASPC (1500 mg/kg) enhanced the immune function of Nile tilapia and improved several immune parameters, including the serum bactericidal activity, phagocytic activity of blood phagocytes, respiratory burst activity of the whole blood, and serum lysozyme activity (Zahran et al. 2014). Moreover, ASPC (1 g/kg) could modulate the intestinal microbiota and activate the immune response to protect grass carp from *Aeromonas hydrophila* infection by increasing the expression of TNF-α, IL-1β, GM-CSF, interleukin enhancer-binding factor 2 homolog, and serine/threonine-protein kinase doublecortin like kinase protein 1 (Shi et al. 2021). ASPC (20–50% of the diet) modulated immunity in *Aeromonas veronii* TH0426 infected crucian carp by increasing the activities of serum acid phosphatase, alkaline phosphatase, and lysozyme and levels of the IL-10, IL-1β, IFN-γ and TNF-α in the spleen (Song et al. 2022). In *Aeromonas hydrophila*-infected mice, ASPC (250 mg/kg) improved the phagocytic activity of neutrophils in intestinal tissues, increased the number of $CD4^+$ T cells in intestinal tissues and thymus, and reduced the number of $CD8^+$ T cells in spleen and thymus (Abuelsaad 2014). ASPC (100–400 mg/kg) modulated immunity in *Vibrio parahaemolyticus*-infected shrimp by increasing the expression of the immune-related factors, including anti-lipopolysaccharide factor, cathepsin B, crustin, lectin, lysozyme, and toll-like receptor (Zhai et al. 2019). In *Brucella*-infected mice, ASPC (50–200 μg/ml) promoted the secretion of proinflammatory cytokines such as TNF-α, IL-12 and IFN-γ and the activation of macrophages, thereby enhancing the host's immune response (Shi et al. 2019). It is widely acknowledged that sepsis is a systemic inflammatory response caused by bacterial infection. Balancing pro- and anti-inflammatory responses is a potential therapeutic approach for sepsis (Johansen et al. 2021). In polymicrobial sepsis mice, ASPC (100–200 mg/kg) increased the percentage of Th1 cells in the spleen and Peyer's patches, decreased the percentage of Treg cells and Th2 cells in the blood circulation, and inhibited the polarization of blood $CD4^+$ T cells towards T helper cell 2 response (Hou et al. 2015).

Mounting evidence suggests that *Astragalus* polysaccharide can be used as an adjuvant for bacterial vaccines. Inactivated *Edwardsiella ictaluri* vaccine, formulated with ASPC (100 μg) as an adjuvant, could improve the survival rate of yellow catfish and protect intestine tissue from the injury of *Edwardsiella ictaluri* by increasing the expression of IL-1β, IL-2, IFN-γ2 and IgM in the spleen (Zhu et al. 2019). Inactivated *Vibrio harveyi* formalin-killed cells vaccine, formulated with ASPC (4 mg/ml) as an adjuvant, could increase IL-1β, IL-16, TNF-α, MHC-Iα and IgM levels in the spleen in groupers (Gwab et al. 2020). For rats vaccinated with recombination urease subunit B, using ASPC (1.25–10 mg/ml) as an adjuvant could increase the levels of ovalbumin-specific IgG in serum and secretory IgA in saliva, vaginal wash and intestinal lavage fluid by activating the TLR2 signaling pathway

and resulting in mixed specific Th1 cells and Th17 cells immune response (Liu et al. 2019a). Overall, these findings indicate that *Astragalus* polysaccharide may be an effective adjuvant for bacterial vaccines.

Pharmacological activities against autoimmune diseases

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system. ASPC (500 mg/kg) could effectively suppress autoimmune encephalomyelitis in mice by inhibiting MOG_{35-55}-specific T cell proliferation, downregulating the levels of IFN-γ, TNF-α, IL-2, and IL-17, upregulating the costimulatory molecules PD-1/PD-Ls signaling pathway, and leading to inhibition of T cell-mediated immune response (Sun et al. 2019). In addition, promoting remyelination is an important strategy for treating multiple sclerosis. In cuprizone-induced demyelination mice, ASPC (500 mg/kg) relieved the neurobehavioral dysfunction and efficaciously facilitated remyelination by activating the Sonic hedgehog signaling pathway and inducing neural stem cells to differentiate into oligodendrocytes (Ye et al. 2021). Systemic scleroderma is an autoimmune disease characterized by fibrotic changes involving excessive collagen deposition in the skin and other organs. ASPC (200 mg/kg) could reduce collagen production and the expression of Smad2 and Smad3 in bleomycin-induced scleroderma mice by suppressing the TGF-β signaling pathway (Hao et al. 2015).

It is widely acknowledged that type 1 diabetes is characterized by the autoimmune destruction of pancreatic β cells. Type 1 diabetes is an autoimmune disease mediated by T cells that destroy insulin-producing β cells in the pancreatic islets (Marfil-Garza et al. 2021). In streptozocin-induced type 1 diabetes mice, ASPC (100–400 mg/kg) could protect pancreatic β cells from apoptosis induced by $CD8^+$ T cells by upregulating the expression of galectin-1 and causing $CD8^+$ T cell apoptosis (Zhou et al. 2011). Li et al. also found that ASPC (100–400 mg/kg) protected β cells from apoptosis in type 1 diabetic rats by downregulating the Th1/Th2 cytokine ratio, decreasing the level of IFN-g and increasing the level of IL-4 by upregulating the peroxisome proliferator-activated receptor γ expression in the spleen (Li et al. 2007).

In type II collagen-induced rheumatoid arthritis rats, ASPC (4 g/kg) reduced paw swelling, serum concentrations of IL-1β and TNF-α, and the levels of NF-κB-p65 and IκBα (inhibitor of NF-κB α) in synovial membranes (Cao et al. 2019a). Moreover, ASPC (10 mg/kg) could mitigate the proinflammatory response, reduce TNF-α, IL-17, and IL-6 levels in myocardial tissues and inhibit the apoptosis in complete Freund's adjuvant-induced rheumatoid arthritis rats by suppressing the activation of TLR4/MAPK/NF-κB signaling pathway (Cao et al. 2019b).

Other pharmacological activities

Astragalus polysaccharides can improve inflammatory response by regulating immune function. In 2,4,6-trinitrobenzene sulfonic acid-induced inflammatory bowel disease rats, ASPC (0.5–1.0 g/kg) could enhance the therapeutic effect of prednisone by promoting the expression of T helper cell 1 and T helper cell 2 specific transcription factors T-bet and GATA-3 (GATA binding protein 3) and ultimately contributing to the transition to the T helper cell 2 phenotype (Gao et al. 2016). In dextran sulfate sodium-induced acute colitis mice, ASPC (100–300 mg/kg) reestablished the immune balance by decreasing the levels of IL-1β, TNF-α, and IL-6 and upregulating IL-22 expression by activating aryl hydrocarbon receptor (present in Th17 cells, Th22 cells or innate lymphoid cells) (Tang et al. 2021). In ovalbumin-induced asthmatic mice, ASPC (100 mg/kg) could promote the therapeutic effect of budesonide by reducing the number of dendritic cells and the levels of IL-4 and IL-10 and increasing the number of Treg cells (Zhang and Ma 2020). Wang et al. found that ASPC (5–15 mg/kg) could reduce eosinophil infiltration and IL-4 expression in the nasal mucosa tissue of ovalbumin-induced asthmatic rats (Wang et al. 2020). Furthermore, Wu et al. documented that ASPC (10–50 mg/kg) attenuated eosinophil and neutrophil-dominant infiltration by reducing the levels of CXCL5, IL-8, CCL20, IL-13RA (IL-13 receptor α) and IL-17RA in ovalbumin-induced asthmatic mice (Lu et al. 2016). Moreover, ASPC (50 μg) has been reported as an adjuvant for the ovalbumin vaccine, which induced Th1 and Th2 immune responses, increased IL-2, IL-4, IL-10, IL-12 and IFN-γ levels and enhanced ovalbumin-specific IgG and IgG1 antibody responses in ovalbumin-induced asthmatic mice (Zhou et al. 2021). Allergic rhinitis is an IgE-mediated chronic inflammatory disease of the allergic nasal mucosa. ASPC (10–50 mg/kg) could improve the inflammatory symptoms of the nasal mucosa and reduce Th2-related cytokines of IL-4, IL-5, and IL-13 levels in serum and nasal mucosa tissue of allergic rhinitis rats by inhibiting the NLRP3 (NLR family pyrin domain-containing protein 3) inflammasome and NF-κB signaling pathway (Xu et al. 2021). In addition, in experimental periodontitis rats, ASPC (50–100 ng/ml) protected the alveolar bone from inflammatory erosion by decreasing the proportion of $CD4^+Foxp3^+$ cells and the levels of receptor activator of NF-κB ligand, osteoprotegerin, TGF-β and IL-10 and upregulating the level of $CD4^+IL\text{-}10^+$ cells in the gingiva (Han et al. 2021). In addition, the pure polysaccharide AMP (20–75 mg/kg) could ameliorate the immunity and spermatogenesis of mice with impaired reproductive function induced by cyclophosphamide by increasing the levels of IL-11, TNF-α and IFN-γ (Qiu and Cheng 2019).

Relationship between the *Astragalus* polysaccharide structure and immunomodulatory effect

Xia et al. compared the immunomodulatory effects of *Astragalus* polysaccharides with different molecular weights (157.7 kDa, 69.9 kDa, 22.4 kDa, 13.2 kDa, and 1.4 kDa) on cyclophosphamide-induced immunosuppression mice. The results showed that the higher the molecular weight, the stronger the phagocytic ability of peritoneal macrophages and the higher the level of secretory IgA in the small intestine (Xia et al. 2011). Li et al. compared the immunomodulatory effects of three *Astragalus* polysaccharides with different molecular weights (> 2000 kDa, 10 kDa and 300 Da) on cyclophosphamide-induced immunosuppression mice. The results showed that the *Astragalus* polysaccharide with a molecular weight of 10 kDa had the best immunomodulatory effect, including promoting the proliferation of T and B lymphocytes and the secretion of IL-2, IL-4, INF-γ and increasing the phagocytic activities of peritoneal macrophages and the activities of spleen natural killer cells (Li et al. 2020b, c). In conclusion, these findings suggest that *Astragalus* polysaccharides with extremely high or low molecular weight exhibit poor immunomodulatory activity. In addition, Ren et al. found that treatment of the *Astragalus* polysaccharide with γ-irradiation (24 kGy) could enhance its immunomodulatory activity on Caco2 cells including promoting NO, TNF-α, IL-1β and IL-8 production via TLR4 signaling pathway activation. Unlike general structural modification, γ-irradiation does not affect the functional groups of polysaccharides but affects physicochemical properties, such as apparent viscosity (Ren et al. 2018). Li et al. subsequently found that γ-irradiation-enhanced *Astragalus* polysaccharide immune activity was associated with decreased molecular weight and viscosity and increased water solubility. γ-irradiated *Astragalus* polysaccharide (300–900 mg/kg) elevated the level of IgA produced by duodenal cells, the jejunal expression of IL-2, IL-10, and IFN-γ, serum IgG concentration, and thymus index, and promoted T and B lymphocytes proliferation in cyclophosphamide-induced immunosuppressed broilers (Li et al. 2019b, c). In addition, *Astragalus* polysaccharides can be chemically modified or functionalized to increase their immunomodulatory activities. In this regard, Se-enriched *Astragalus* polysaccharide nanoparticles showed a stronger ability to enhance T lymphocyte proliferation than *Astragalus* polysaccharides in vitro (Meng et al. 2018). In short, the relationship of *Astragalus* polysaccharide structure on immunomodulatory effect warrants further research in the future.

Conclusion and perspectives

In short, *Astragalus* polysaccharide is a valuable immunomodulatory medicine. Table 1 summarizes the immunomodulatory effect, and Fig. 1 summarizes the molecular mechanism. *Astragalus* polysaccharide can improve immunosuppression caused by drugs in central immune organs and peripheral immune organs, including bone marrow, thymus, lymph nodes, spleen and mucosal tissues. Since these immune organs are the sites where various immune cells differentiate, mature and produce an immune response, *Astragalus* polysaccharide can further regulate the activity of a variety of immune cells. These immune cells include macrophages, natural killer cells, dendritic cells, T lymphocytes, B lymphocytes and microglia. *Astragalus* polysaccharides can induce these immune cells to produce a variety of cytokines and chemokines, thereby enhancing the immune response. The immunomodulatory effect of *Astragalus* polysaccharide makes it useful for the treatment of various diseases, including cancer, infection, type 1 diabetes, asthma, and autoimmune disease. Among these, the anticancer effect of *Astragalus* polysaccharide is the most prominent, which is closely related to its activation of tumor immune response and inhibition of tumor immune escape.

Although the current research has deeply explored the immunomodulatory effect of *Astragalus* polysaccharide, there are few studies on the relationship between polysaccharide structure and immunomodulatory activity. Table 2 summarizes the structural information of these pure polysaccharides with immunomodulatory effects and hopes to provide useful information for further research. In addition, there are few reports on structure modification of *Astragalus* polysaccharides. Therefore, the immunomodulatory function of different modified *Astragalus* polysaccharides can be investigated in the future. At present, although there are many experimental studies on the immunomodulation of *Astragalus* polysaccharides, there is still a lack of sufficient clinical research. Insufficient studies on the structural characteristics of *Astragalus* polysaccharides may be the key to restricting clinical research. Therefore, conducting more clinical research based on sufficient structural characterization studies in the future may be an important research direction.

Table 1 The pharmacological effect of *Astragalus* polysaccharide

Name	Models	Dosages	Immunomodulatory actions	References
ASPC	Ovalbumin subcutaneously immunized mice	1–4 mg/ml	Promote splenocytes proliferation and IFN-γ and IL-6 secretion and enhance the specific immunoglobulins antibody response	Fan et al. (2013)
	MCF-7 human breast cancer cell	100–1000 μg/ml	Induce cancer cell apoptosis by activating RAW 246.7 macrophages	Li et al. (2018a)
	Cyclophosphamide-induced mice	50–80 mg/kg	Increase the serum level of immunoglobulin and inhibit IL-2 overproduction	Meng et al. (2017)
	Ovalbumin-induced asthmatic mice	100 mg/kg	Reduce the number of dendritic cells and the levels of IL-4 and IL-10 and increase the number of anti-inflammatory natural killer cells and Treg cells	Zhang and Ma (2020)
	Radiation-induced mice	50–500 mg/kg	Promote colony formation and attenuate megakaryocyte apoptosis	Li et al. (2021a)
	Streptozocin-induced type 1 diabetes mice	100–400 mg/kg	Protect pancreatic β cells from apoptosis by up-regulating the expression of galectin-1 and causing $CD8^+$ T cell apoptosis	Zhou et al. (2011)
	Polymicrobial sepsis mice	100–200 mg/kg	Increase the percentage of T helper cells, decrease the percentage of Treg cells, and inhibit the polarization of blood $CD4^+$ T cells toward a T helper cell 2 response	Hou et al. (2015)
	Inflammatory bowel disease rats	0.5–1.0 g/kg	Promote the expression of T helper cell 1 and T helper cell 2 specific transcription factors	Gao et al. (2016)
	Cyclophosphamide-induced mice	600 mg/kg	Increase the expression of IgA, IgG, IgM, IL-6, IFN-γ, complement 3, complement 4 and TNF-α	Yu et al. (2016)
	Rats vaccinated with regeneration Urease subunit B	1.25–10 mg/ml	Result in mixed specific helper T 1 cells and helper T 17 cells immune response and contribute to the inhibition of *Helicobacter pylori* colonization	Liu et al. (2019a)
	Cyclophosphamide-induced rats	100 mg/kg	Improve the chemotactic capacity of polymorphonuclear leukocytes	Zhang et al. (2015)
	RAW264.7 macrophages	12.5–100 μg/ml	Increase the production of NO, IL-1β, IL-6 and TNF-α	Zhao et al. (2011)
	H22 tumor-bearing mice	10–100 mg/kg	Up-regulate the expression of MICA and MICB on the surface of tumor cells and activate natural killer cells	Mu et al. (2019)
	Brucella-infected mice	50–200 μg/ml	Promote the activation of macrophages and the production of pro-inflammatory cytokines	Shi et al. (2019)
	HSV-1 infected mouse astrocytes	120 μg/ml	Increase the expression of TNF-α and IL-6 by activating the TLR3/NF-κB signaling pathway	Shi et al. (2014)
	Zebrafish infected by the spring viremia of carp virus	0.01%	Up-regulate anti-inflammatory cytokine IL-10, tight junction protein 1b, and occludin1, and increase the expression of antiviral genes in the spleen	Li et al. (2021b)
	Aeromonas hydrophila-infected mice	250 mg/kg	Down-modulate the phagocytic activity of neutrophils, increased the number of $CD4^+$ T cells and reduce the number of $CD8^+$T cells	Abuelsaad (2014)

Table 1 (continued)

Name	Models	Dosages	Immunomodulatory actions	References
	Mice vaccinated with HBV-DNA vaccine	500 μg/mouse	Increase the proliferation activity of T lymphocytes, induce $CD4^+$ T cells to produce IL-4, IL-2 and IFN-γ and enhance the expression of IFN-γ in $CD8^+$ T cells	Du et al. (2012)
	Mice dendritic cells	50–200 μm/ml	Induce the differentiation of splenic dendritic cells to $CD11c^{high}$ $CD45RB^{low}$ dendritic cells	Liu et al. (2011)
	Spleen deficiency syndrome mice	300–1200 mg/kg	Increased the percentage of $CD3^+$ T cells, the percentage of $CD3^+$ $CD4^+$ T cells and the ratio of $CD3^+CD4^+$ to $CD3^+CD8^+$, and reduced the expression of IL-6, IL-10 and TNF-α	Zhao et al. (2019)
	Non-small cell lung cancer-bearing mice	3 mg/kg	Promote the functional maturation of dendritic cells and enhance the anti-cancer immune response mediated by T cells	Bamodu et al. (2019)
	53 patients with lung cancer	500 mg/person	Normalize the neutrophil-to-lymphocyte ratio of lung cancer patients treated with immune checkpoint inhibitors	Tsao et al. (2021)
	Tumor-bearing mice	50 mg/kg	Down-regulate the expression of PD-L1	Chang et al. (2020b)
	4T1-bearing mice	100–200 μg/ml	Enhance the expression of CD40, CD80 and CD86 markers, up-regulate the expression of immunomodulatory cytokines and chemokines	Chang et al. (2015)
	Human hepatocellular carcinoma	10–200 μg/ml	Inhibit the activation of $CD4^+CD25^+$Treg cells by restoring cytokine imbalance and reducing FOXp3 expression	Li et al. (2012)
	S180 Sarcoma-Bearing Mice	40–80 μg/ml	Promote the proliferation of γδ T cells and induce the expression of IFN-γ, FasL and granzyme B	Sun et al. (2014)
	MCF-7 human breast cancer cell	100–100 mg/ml	Activating RAW 264.7 macrophages and promote the expression of NO and TNF-α	Li et al. (2019d)
	EAC tumor-bearing mice	500 mg/kg	Activate macrophages RAW 264.7 by activating the TLR4/MyD88-dependent signaling pathway	Zhou et al. (2017)
	4T1 tumor-bearing mice	50 μg/ml	Induce low-dose anti-PD-1 antibody responses	Chang et al. (2020a)
	Type 1 diabetic rats	100–400 mg/kg	Protect β cells from apoptosis by downregulating the Th1/Th2 cytokine ratio	Li et al. (2007)
	Melanoma-bearing mice	50–200 mg/kg	Reduce the number of myeloid-derived suppressor cells, as well as the expression of related molecule Arg-1 and cytokines IL-10 and TGF-β	Ding et al. (2021).
	HeLa cervical cancer cells	15–1000 μg/ml	Increase peripheral blood mononuclear cells number and decrease myeloid-derived suppressor cells number	Shokati et al. (2021)
	Rat microglia	0.1 mg/ml	Inhibit M1 polarization and promote M2 polarization	Jia et al. (2022)
	Mice treated with a high-fat diet and streptozotocin	500 mg/kg	Reduce metabolic stress-induced astrogliosis and microglial activation	Huang et al. (2017)
	Rat microglia	200 μg/ml	Inhibition of NF-κB and AKT signaling pathways	Luo et al. (2015)
	Bone marrow mesenchymal stem cells	50 μg/ml	Inhibit the production of reactive oxygen species and the activation of mitochondrial apoptotic pathway	Zhang et al. (2020b)

Table 1 (continued)

Name	Models	Dosages	Immunomodulatory actions	References
	Muscovy ducklings	0.6 mg/ml	Increase the levels of IL-4, IL-6, IL-15, TNF-α, and INF-γ	Liao et al. (2021)
	Primary head kidney macrophages	6.25–100 μg/ml	Increase the expression of IL-1β, IL-6, IL-8, TNF-α, IFN-γ and iNOS	Zhang et al. (2020a)
	Porcine alveolar macrophages	10–30 μg/ml	Inhibit the expression of IL-1β, IL-6 and TNF-α	Liu et al. (2018b)
	Dendritic cells	0.40–2.80 mg/ml	Up-regulate the expression of MHC-II, CD80 and CD86	Xiong et al. (2020)
	Microglia	200 μg/ml	Inhibit the expression of various pro-inflammatory factors	Luo et al. (2015)
	Cancer patients	250–500 mg/day	Inhibit the expression of immunosuppressive factors IL-10 and IL-12	Huang et al. (2019)
	S180 tumor-bearing mice	150–300 mg/kg	Regulate the percentages of $CD3^+$, $CD4^+$, $CD8^+$ T cells and $CD19^+$ B cells	Yu et al. (2021)
	Co-culture of peripheral blood mononuclear cells and HeLa cells	15–1000 μg/ml	Increase the number of peripheral blood mononuclear cells and decrease the number of myeloid-derived suppressor cells	Shokati et al. (2021)
	Melanoma-bearing mice	50–200 mg/kg	Reduce myeloid-derived suppressor cells number and the expression of molecule Arg-1 and cytokines IL-10	Ding et al. (2021)
	Goslings infected with parvovirus	0.3 ml	Decrease the expression of secreted immunoglobulin A, IL-1β, IL-6 and TNF-α and increase the levels of serum IgG, IgM, complement 3, complement 4, IFN-γ	Luo et al. (2021)
	Hatched chicks	0.5 ml	Increase the concentrations of IFN-γ, IL-2, IL-4 and IL-6, promote lymphocyte proliferative capability and the frequencies of $CD4^+$ and $CD8^+$ T cells	Xue et al. (2020)
	Groupers	4 mg/ml	Increase IL-1β, IL-16, TNF-α, MHC-Iα and IgM levels	Gwab et al. (2020)
	Autoimmune encephalomyelitis	500 mg/kg	Inhibit MOG_{35-55}-specific T cell proliferation, down-regulate proinflammatory cytokines, up-regulate the costimulatory molecules PD-1/PD-Ls signaling pathway	Sun et al. (2019)
	Type 1 diabetic rats	100–400 mg/kg	Protect β cells from apoptosis	Li et al. (2007)
	Rheumatoid arthritis rats	4 g/kg	Reduce paw swelling, serum concentration of IL-1β and TNF-α, and the levels of NF-κB-p65 and IκBα	Cao et al. (2019a)
	Acute colitis mice	100–300 mg/kg	Up-regulate the IL-22 level by activating aryl hydrocarbon receptor	Tang et al. (2021)
	Experimental periodontitis rats	50–100 ng/ml	Decrease the proportion of $CD4^+Foxp3^+$ cells and up-regulate the level of $CD4^+IL\text{-}10^+$ cells	Han et al. (2021)
	Allergic rhinitis rats	10–50 mg/kg	Inhibit NLRP3 inflammasome activation and NF-κB signaling pathway	Xu et al. (2021)
	Mice splenic lymphocytes	1–500 μg/ml	Enhance lymphocytes proliferation and increase T-cell $CD4^+/CD8^+$ ratio	Xu et al. (2019)
	Broiler chickens	10 g/kg	Increase serum IFN-α and IFN-β levels and activate the TLR4 signaling pathway	Li et al. (2018b)
	RAW 264.7 macrophages	25 μg/ml	Increase the levels of NO, diglycerides, inositol 1, 4, 5-triphosphate, and cyclic adenosine monophosphate	Wang et al. (2017)

Table 1 (continued)

Name	Models	Dosages	Immunomodulatory actions	References
	Alveolar macrophages	200 mg/kg	Decrease the levels of IL-6, IL-8, and TNF-α	Chu et al. (2016)
	Breeder cock testes	10 g/kg	Reduce levels of IFN-γ, perforin, the DNA-binding protein HMG-2 and lysin	Wu et al. (2017)
	Mice dendritic cells	10 mg/kg	Induce cytotoxic T lymphocyte activation and immune factor TNF-α, IFN-γ, IL-4, IL-10, and IgG1 production	Xiong et al. (2020)
	Experimental autoimmune encephalomyelitis mice	0.4–0.8 mg/ml	Reduce the secretion of inflammatory factors IL-1α, TNF-α and C1q, and inhibited the activation of neurotoxic astrocytes	Liu et al. (2021)
	H22 tumor-bearing mice	50–400 mg/kg	Increase the spleen and thymus indexes and promote T lymphocytes to produce IL-2, IL-6 and TNF-α	Lai et al. (2017)
	4T1-bearing mice	10 mg/kg	Inhibit the production of VEGF and induce the production of scFv 4E	Lee et al. (2020)
	Porcine endothelial cells	10 μg/ml	Increase the levels of IFN-α, IFN-β, IL-1, IL-6, and IL-8	Zhuge et al. (2017)
	Crucian carp	2 g/kg	Up-regulate IgM, IL-8, IL-10, IL-1β, IFN-α, IFN-γ, MyD88, TGF-β and TNF-α expression	Liu et al. (2022)
	Crucian carp	20–50% of the diet	Increase activities of serum acid phosphatase, alkaline phosphatase, and lysozyme and levels of the IL-10, IL-1β, IFN-γ and TNF-α	Song et al. (2022)
	Nile tilapia	1500 mg/kg	Enhance phagocytic activity of blood phagocytes, respiratory burst activity of whole blood, and serum lysozyme and bactericidal activities	Zahran et al. (2014)
	Scleroderma mice	200 mg/kg	Reduce collagen production and the expression of Smad2 and Smad3	Hao et al. (2015)
	Rheumatoid arthritis rats	10 mg/kg	Reduce TNF-α, IL-17, and IL-6 levels and inhibited the apoptosis of cardiac tissues	Cao et al. (2019b)
	Asthmatic mice	10–50 mg/kg	Reduce the levels of CXCL5, IL-8, and CCL20 and the levels of IL-13RA and IL-17RA	Lu et al. (2016)
RAP	RAW264.7 macrophages	30–300 μg/ml	Promote the production of NO, TNF-α and IL-6 by the activation of NF-κB and MAPK signaling pathways	Wei et al. (2016)
	Paclitaxel induced-RAW264.7 macrophages	10–100 μg/ml	Avoid apoptosis and cell cycle arrest	Bao et al. (2018)
	RAW264.7 macrophages	30–300 μmol/L	Induce macrophage's polarization to M1 phenotype by inducing higher expression of M1 marker genes	Wei et al. (2019)
	RAW264.7 macrophages	30–300 μg/ml	Promote the production of NO, TNF-α and IL-6	Li et al. (2017)
AMP	C57BL/6 mice	100–500 mg/kg	Increase the levels of co-stimulatory and MHC I and MHC II and promote the production of pro-inflammatory cytokines	Lim et al. (2021)
	Mouse natural killer cells	10–100 μg/ml	Promote the expression of IFN-γ, TNF-α, Granzyme-B, and NKp44	Li et al. (2020a)
	RAW264.7 macrophages	10–100 μg/ml	Stimulate to produce NO by activating the NF-κB and MAPKs signaling pathways	Li et al. (2020a)
	Cyclophosphamide induced-mice	20–75 mg/kg	Increase the levels of IL-11, TNF-α and IFN-γ	Qiu and Cheng (2019)

Table 1 (continued)

Name	Models	Dosages	Immunomodulatory actions	References
APSII	RAW264.7 macrophages	10–80 μg/ml	Increase the expression of MHCII, CD40, CD80 and CD86	Lv et al. (2016)
	Mice dendritic cells	1.67–45 μg/ml	Induce the production of NO and increase the expression of CD40, CD80, CD86 and MHCII	Zhu et al. (2016)
AP	B16 tumor-bearing mice	10 g/kg	Promote the proliferation of thymocytes and spleen cells, and the activity of natural killer and T cells	Wu et al. (2016)
AP-I	Gastric cancer rats	300 mg/kg	Promote the proliferation of rat spleen lymphocytes and increase the levels of IL-2, IgA, IgG and IgM	Li et al. (2009)
APS	Lung metastatic melanoma mice	50 mg/kg	Activate the dendritic cells, cytotoxic T lymphocytes, and natural killer cells of the mesenteric lymph nodes	Hwang et al. (2021)
APS-I and APS-II	Cyclophosphamide-induced mice	5–20 mg/kg	Increase the number of white blood cells, lymphocytes, monocytes and neutrophils and the expression of IL-2, IL-6, and GM-CSF	Li et al. (2020d)
APS-III	Doxorubicin hydrochloride-treated lung cancer mice	15%	Increase the expression of IL-2, TNF, IFN-γ, and IL-17 A and the $CD4^+/CD8^+$ ratio, promote the activity of spleen cells and thymocytes and decrease IL-10 level	Zhou et al. (2018)
APS-IV	Mice spleen T and B cells	50–200 μm/ml	Stimulate the proliferation of mouse T cells and B cells	Niu et al. (2011)
AX-I-3b	Cisplatin-treated lung cancer mice	50–200 mg/kg	Increase the levels of cytokines IL-2, IL-6 and TNF-α, and the ratio of $CD4^+$T cells to $CD8^+$ T cells	Li et al. (2019a)
AMA-1-b-PS2	C3H/HeJ mice	10–100 μg/ml	Contribute to immunomodulation of Peyer's patch cells in the mouse small intestine by activating the T cell response	Lim et al. (2016)
cAMPs-1 A	H22 tumor-bearing mice	75–300 mg/kg	Promote the activity of macrophages, natural killer cells and T lymphocytes	Liu et al. (2018a)
ASP	H22 tumor-bearing mice	100–300 mg/kg	Increase the level of TNF-α, IL-2 and IFN-γ and the activity of macrophages, lymphocytes and natural killer cells	Yu et al. (2018)
AP	BALB/c mice	300 mg/kg	Promote macrophage's phagocytosis and the secretion of immune-related cytokines	Peng et al. (2019)
APS-V and APS-VI	Mice spleen T and B cells	50–200 μm/ml	Stimulate the proliferation of mouse T cells and B cells	Jiang et al. (2016)

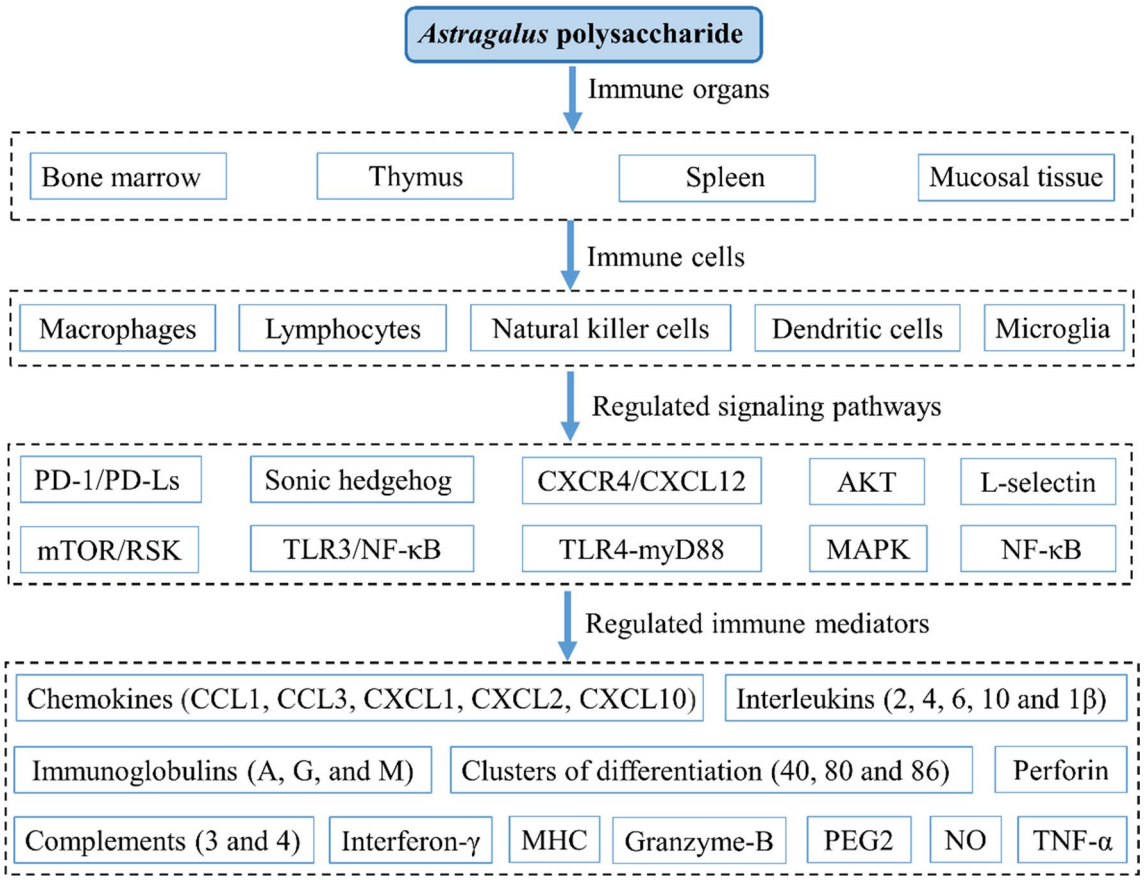

Fig. 1 The immunomodulatory effect and molecular mechanism of *Astragalus* polysaccharide

Table 2 The pure polysaccharide with immune stimulating effect extracted from *Astragalus*

Name	M.W. (kDa)	Monosaccharide composition	Main structure	References
APS-I	> 500	Glc: Gal: Ara: Rha: GalA = 1.5:1:5.4:0.08:0.1	ND	Li et al. (2020d)
APS-II	10	Glc: Gal: Ara: Rha: GalA = 9:1:1.4:0.04:0.001	ND	Li et al. (2020d)
APS-III	ND	Glc, Xyl, Gal and GalA	Backbone composed of Glc(1–4), Xyl(1–2), Gal(1–4), and GalA(1–3)	Zhou et al. (2018)
AX-I-3b	7.87	Ara: Xyl: Glc = 10.4:79.3:1.1.	ND	Li et al. (2019a)
APS	17.39	Glc: Ara: Xyl: Man: Gal = 95.0:2.9:0.7:0.7:0.6	ND	Hwang et al. (2021)
AMA-1-b-PS2	ND	Ara: Fuc: Gal: Glc: Man: Rha: Xyl: GalA: GluA: GlcA = 12.8:4.5:25.6:23.6:24.8:5.1: 0.7:1.5:1.5:1.4	The backbone is composed of β-D-(1→3) linked galactans	Lim et al. (2016)
APSII	11.4	Xyl: Glu: Ara: Rha: Man: Gal = 9.22:77.89:1 :5.18:4.54:2.17	ND	Lv et al. (2016)
APS-IV	20.7	Glc	The backbone is composed of α-1,4-linked-D-glucose	Niu et al. (2011)
AP	ND	Glc	The backbone is composed of α-D-glucose	Peng et al. (2019)
AP-I	ND	Glc	The backbone is composed of α-1,4-linked-D-glucose	Li et al. (2009)
AMP	804	Glc: Ara: Gal = 91.0:6.2:2.8	ND	Li et al. (2020a)
RAP	1334	Rha: Ara: Glc: Gal: GalA = 0.03:1.00:0.27:0.36:0.30	Backbone consists of 1,2,4-linked Rha*p*, α-1,4-linked Glc*p*, α-1,4-linked GalA*p*6Me, β-1,3,6-linked Gal*p*, with branched at *O*-4 of the 1,2,4-linked Rha*p* and *O*-3 or *O*-4 of β-1,3,6-linked Gal*p*	Yin et al. (2012)
cAMPs-1 A	12.3	Fuc: Ara: Gal: Glc: Xyl = 0.01:0.06:0.20:1.00:0.06	ND	Liu et al. (2018a)
APS-V	40.1	Ara	ND	Jiang et al. (2016)
APS-VI	15.3	Rha: Glc: Gal: Ara = 1:10.76:6.55:12	ND	Jiang et al. (2016)
ASP	2.1	Ara: Gal: Glc: Man = 1.00:0.98:3.01:1.52	ND	Yu et al. (2018)

Ara arabinose, *Fuc* fucose, *GluA* glucuronic acid, *Xyl* xylose, *Man* mannose, *Glc* glucose, *Gal* galactose, *Rha* rhamnose, *GalA* galacturonic acid, *ND* not detected

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Declarations

Conflict of interest There is no conflict of interest to declare.

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