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# Advances on immunoregulation effect of astragalus polysaccharides

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*Astragalus membranaceus* (AM) is a traditional chinese medicine (TCM) with active substances such as saponins and polysaccharides, The most abundant active ingredient is astragalus polysaccharides (APS). It is a natural extract with multiple activities such as anti-viral, anti-tumor and the immune-enhancing effects. In recent years, studies on the role of APS in immunomodulatory direction have been increasing, and numerous studies have shown that APS has a better immune enhancing effect. This paper outlines the immunomodulatory effects of APS in terms of immune cells, nonspecific immunity, anti-viral immunity, anti-tumor effects, and applications in animal production, which would provide a base for the further applications of APS. Herein, this current review intends to describe the immunomodulatory effects of APS with underlying mechanisms of therapeutic effects.

## KEYWORDS

astragalus polysaccharides, immunomodulation, anti-viral immunization, anti-tumor, overview

## Introduction

In China, *A. membranaceus* (AM) which also known as Huangqi, is derived from the dried root of the perennial legume *A. membranaceus* Bge. var. *mongholicus* (Bge.) Hsiao and *A. membranaceus* (Fisch.) Bge. It is a perennial traditional chinese medicine (TCM) that belongs to the legume family, mainly distributed in Shanxi province, Liaoning province, Neimenggu province, and other province (Ma et al., 2019) which have a cold temperate zone. *Astragalus* is a TCM with diuretic, anti-aging, and anti-hypertensive effects (Wang et al., 2022). Moreover, AM has been included in the list of national drug and food homology in 2018 (Tian et al., 2020). *Astragalus* contains a variety of active ingredients, including polysaccharides, saponins, flavonoids, amino acids, and a variety of trace elements (Li et al., 2009; T et al., 2009; Zhang et al., 2012).

In recent years, pharmacological studies on AM, especially the immunomodulatory effects of APS, have become a hot topic. Numerous studies have demonstrated that APS has significant immunomodulatory effects both *in vivo* and *in vitro* in immunosuppression animal models (Li et al., 2020), and it also enhances the immune effects of normal animals

(Angela et al., 2020). The fundamental mechanisms of the APS include organ immunity, regulation of the immune-related genes, immune cells, and synergistic effects of *Astragalus* with other TCM. This review will overview the immunomodulatory effects of APS.

## Effects of APS on non-specific immune cells

### The effects of APS on macrophages

Macrophages are important cells in the body's non-specific immunity, providing an effective defense system for tumor cells, parasites, and fungi against the host body cells (Wang et al., 2015). Its phagocytic ability can reflect the immune capacity of the body (Jin et al., 2014), APS improves macrophage function and enhances phagocytosis of macrophages. APS can increase the secretion of TNF- $\alpha$  and nitric oxide, promote the increase of macrophages, and protect macrophages' integrity (Shi et al., 2019). Chai et al. (2019) found that intraperitoneal injection of 2 mg/ml APS in mice for 7 days could significantly increase the polarization of M1-type peritoneal macrophages in mice. Yang et al. (2013) found that 100 and 400 mg/kg APS could significantly enhance the phagocytic function of peritoneal macrophages in H22 liver cancer mice and inhibit the growth of solid hepatoma tumors. These results suggested that APS can enhance immunomodulatory effects by stimulating macrophage activity.

### Effects of APS on dendritic cells and erythrocytes

Dendritic cells (DCs) help to regulate autoimmune and other immune responses (Iberg and Hawiger, 2020). Red Blood Cells (RBC) are emerging as important modulators of the innate immune response (Anderson et al., 2018). APS can promote the maturation and differentiation of DCs by upregulating CD36 and IL-27 and downregulating IFI16, thus positively influencing the development and progression of atherosclerosis (Chen et al., 2015). Shao et al. (2006) investigated the regulatory effects of APS on the maturation and the function of cultured mouse bone marrow-derived DCs, showing that APS could increase the co-expression of CD-11c and primary histocompatibility complex class II molecules on DC surface, the 100  $\mu$ g/ml is the optimal dose, After using the APS treatment, the DCs showed a more mature morphology with longer projections. APS may enhance the immune adhesion of chicken erythrocytes by affecting the activity or number of complement receptors on the erythrocyte membrane (Li et al., 2007a).

## Effects of APS on specific immune cells

The effects of APS on specific immune cells are mainly reflected in the increase of proliferation and differentiation of B and T lymphocytes, and the increase of serum antibody concentration, the proliferation of lymphocytes can reflect the state of cellular immunity (Lin et al., 2015). Studies have shown that *Astragalus* polysaccharide inhibits the increase of Tregs in immunosuppression models and melanoma models (Sun et al., 2013). Nie et al. (2004) reported that APS significantly promoted Con A-induced proliferative responses in mouse splenic T lymphocytes and thymic T lymphocytes. The highest value of T lymphocytes was observed at 50  $\mu$ g/ml for APS. Li et al. (2007b) found a downregulation of the Th1/Th2 cytokine ratio in mice injected with APS. By grouping 100 patients with diabetic nephropathy (DN), Zhang et al. (2022) added APS injection therapy to the observation group. 14 days later found that *astragalus* polysaccharide reduced BUN, Cr, Th1, Th2 levels, and NLR, Th1/Th2 values in DN patients and was more effective than conventional Western medicine alone. Wang et al. (2007) reported that APS could induce the proliferation of B and T lymphocytes through synergistic Lipopolysaccharides (LPS) and ConA at the appropriate doses.

## Effects of APS in anti-viral immunity

Antiviral immunity is an important immunity of the organism against viruses and is one of the main bases of adaptation to the natural environment, and its immune pattern includes both cellular and humoral immunity (Huang et al., 2015). It has been demonstrated that antiviral immunity is closely related to CTL cells (cytotoxic T lymphocytes), CD3<sup>+</sup> CD4<sup>+</sup> (helper/inducer T lymphocytes) and cytokines such as IL, IFN- $\gamma$ , nuclear transcription factor (NF)- $\kappa$ B.

APS has a wide range of anti-viral applications; not only can prevent viral infections in humans and prevent many animal viruses. Studies have shown that APS can prevent hepatitis B virus (HBV) and effectively inhibit the proliferation of HepG2 2.2.15 cells (Zou et al., 2003). APS has an inhibitory effect on HBV replication *in vivo* and can be used as a supplementary modality in treating of hepatitis B infection (Dang et al., 2009). In addition, APS can also be used as a potent adjuvant for the hepatitis B DNA vaccine (Du et al., 2012). APS, as a vaccine adjuvant, has advantages of low toxicity and hypoallergenic (Wei et al., 2002). APS also has significant resistance to Herpesvirus, which can cause a variety of diseases such as herpes, rashes, tumors, and other diseases (Gable et al., 2014). APS can block the replication of Epstein-Barr virus (EBV) and exert anti-EBV effects (Guo et al., 2014).

In addition, APS plays an important role in the treatment of coronavirus disease 2019 (COVID-19). Since the outbreak of

COVID-19, it has rapidly swept the world. In China, TCM has played an essential role in preventing and treating this new coronavirus pneumonia outbreak. A comprehensive review of the available literature revealed that AM could be used to treat COVID-19 in all periods (He et al., 2020). Zhao et al. (2020) collected 64 drugs to prevent COVID-19 in various provinces and found that AM was used most frequently. Clinical data disclosed by government departments and regions indicate that the combined treatment of COVID-19 with Chinese and Western medicine is effective. There may be a positive correlation between the cure rate of patients and the participation rate of Chinese medicine treatment.

## Immunomodulatory effects of APS anti-tumor

At present, tumor has become one of the diseases with the highest mortality rate, and the incidence and death rate of tumor in China are on the rise, which seriously endangers people's health. Tumors are formed by excessive and abnormal proliferation of local tissue cells under the prolonged stimulation of various intrinsic or extrinsic factors (Kankuri et al., 2005). It is widely used APS in the clinical treatment of diseases, especially the research related to anti-tumor effects, which is gaining attention. In recent years, numerous academic studies on the tumor immune mechanism of APS have found that the enhancing effects of APS are mainly related to T-lymphocyte (T cells), DCs, interferon (IFN), TNF- $\alpha$ , interleukin cells (IL), and so forth.

## APS enhances the anti-tumor immune function of the body

The immune function of the body is closely related to tumorigenesis (Zhang and Zhao, 2012). In tumor tissues, the number of Th1 cells decreases, and T cells' immune function is reduced. APS can promote T cells proliferation and induce Th1/Th2 to Th1 transition. Moreover, APS can induce DCs maturation and enhance the body's anti-tumor immune function (Bo et al., 2015; Jing et al., 2021). Regulatory cells (Treg) can suppress T cell activation and value-added, and APS can inhibit tumor production by reducing Treg numbers in the spleen (Sun et al., 2013). Lai et al. (2017) administered APS at different doses to hepatocellular carcinoma H22-bearing mice to investigate their anti-tumor effects, and results showed that APS could inhibit the growth of H22 cells and the concentration of IL-2, IL-6, and TNF- $\alpha$  cytokines increased significantly, indicating that APS could affect immune regulation and suppress tumors. CD4<sup>+</sup>/CD8<sup>+</sup> in a stable state can maintain the body's immune function (Saber et al., 2016), however, the immune function of cancer patients is suppressed, and the T cells

ratio is imbalanced. Hence, it is crucial to maintain the CD4<sup>+</sup>/CD8<sup>+</sup> balance (Song et al., 2015). Getachew et al. (2014) also demonstrated that APS significantly increased lung cancer patients' CD3<sup>+</sup>, CD8<sup>+</sup>, CD4<sup>+</sup>, and CD4<sup>+</sup>/CD8<sup>+</sup>.

## Anti-tumor clinical applications

Cancer has always been a disease with a high clinical mortality rate, and the treatment for cancer patients is still mainly surgical, but the risk of surgery is high. Clinical research on TCM against cancer has been conducted for many years, and studies have found that *Astragalus* has an intervention effect on many types of tumors. The use of APS injection combined with chemotherapy, radiotherapy, and other clinical use of tumor achieved better efficacy. Li and Yu (2019) have found that Patients who used APS injection were found to have significantly increased disease control and treatment efficiency. APS injection increased CD4<sup>+</sup>/CD8<sup>+</sup> and completely reversed tumor progression.

On the clinical effects of APS injection used together with chemotherapy, Lin et al. (2009) observed the efficacy of 40 patients with malignant tumors treated with APS injection combined with chemotherapy for one course (21 days). The cure rate was 70%, higher than the chemotherapy group (50%). Combining APS injections with chemotherapy is more effective than chemotherapy alone in cure rates and improved body function. Radiation therapy is also an essential tool in the treatment of tumors. Yu (2013) found that the use of APS injection could weaken bone marrow hematopoiesis in patients with non-small cell lung cancer caused by radiotherapy, maintain the hematopoietic microenvironment, and enhance the immune level of patients. Radioactive particle implantation combined with APS injections can improve the physical status, lower serological tumor markers, and improve immunity (Sun et al., 2014). APS combined with infrared (IR) treatment increased the sensitivity of human nasopharyngeal carcinoma to IR and indirectly increased the number of apoptotic cancer cells (Zhang et al., 2020).

## Effects on expression of related genes

The immunomodulatory effect of APS is attribute to its ability to promote the synthesis of DNA, RNA, and proteins in cells and regulate the expression of relevant genetic material. As an immunomodulator related to Foot and mouth disease (FMD) vaccine, Li et al. (2011), found that APS can increase the titer of specific antibody and up-regulated mRNA expression of IFN- $\gamma$  and IL-6. Liu et al. (2015) found that APS could reduce lipopolysaccharide-induced immune stress in chickens by decreasing gene transcription of Toll-like receptor 4 (TLR4) and NF- $\kappa$ B. Yuan et al. (2008) also found that APS can

TABLE 1 APS in combination with other ingredients and applications.

Extract composition	Role	Research conclusion	References
APS and ginseng polysaccharides (GPS)	Animal breeding	Increase body weight, feed conversion and reduce the dependence on antibiotics in Weaned Piglets	Yang et al. (2019)
APS and GPS	Animal breeding and Vaccine booster effect	Improve immunity and can also be used as H5N1 vaccine adjuvants	Abdullahi et al. (2016)
APS and GPS	Enhanced growth performance	Enhanced piglet growth performance, alleviated liver dysfunction and intestinal barrier function	Wang et al. (2020)
APS, chlorogenic acid, and allicin	Animal breeding	Helped to boost immunity, antioxidant capacity and disease resistance of shrimp without biomolecule damage	Huang et al. (2018)
APS and Soybean Isoflavone	Animal breeding	Improve the average daily feed intake, lactation yield, serum antioxidant activity, immune function, and the hormone levels of lactating sows, and the optimum dosage in this study was 200 mg/kg	Wu et al. (2021)
APS and chitoooligosaccharides	Animal breeding	Burst activity (RBA), phagocytic activity (PA), lysozyme activity, and superoxide dismutase (SOD) activity	Lin et al. (2017)
APS and polysaccharopeptide (PSP)	Immunoregulatory and anti-tumor effects	Increase the percentage of CD3 (+) and CD4 (+) T-lymphocytes, the ratio of CD4 (+)/CD8 (+), and the expression of IL-2/IL-2R in spleen and Bax in tumor tissue	Jin et al. (2008)
APS and PSP	Anti-tumor effects	Increase CD4 (+)/CD8 (+) ratio, TNF, IFN-gamma, IL-2, and IL-17A in immunosuppressive mice and lung cancer mice ( $p < 0.05$ ), The PSP + APS herbal formula has immunomodulatory effects and anti-tumor activity in mice	Zhou et al. (2018)

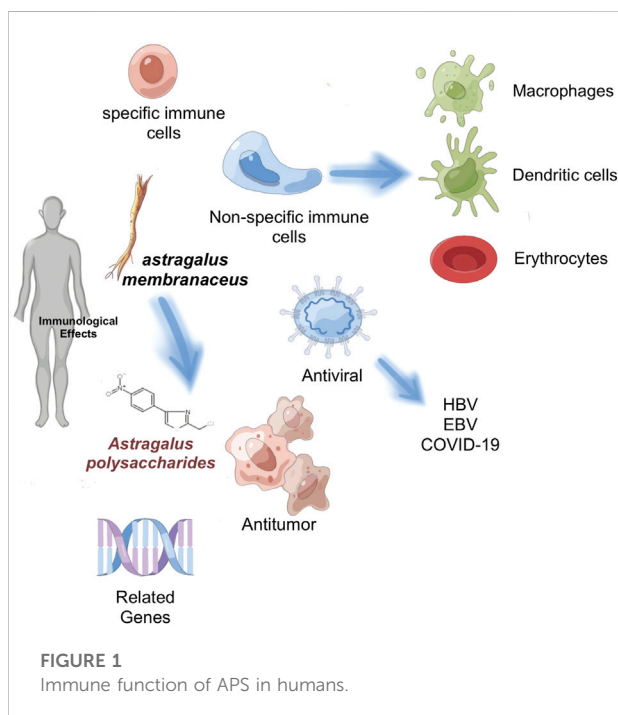
regulate immune gene expression in the head and kidney of carp. APS can enhance the protective immunity of the body against toxoplasmosis by regulating the relevant immune genes and also provides a new idea for the control of *Toxoplasma gondii* (Yang et al., 2010).

## The effects of *Astragalus* complex

*Astragalus* can be used in combination with various TCM to enhance the immune function. AM can be used with other TCM, for example, *Echinacea*, *Astragalus*, and *Glycyrrhiza* herbal tinctures stimulated immune cells, can be quantified by CD69 expression of CD4 and CD8 T cells (Brush et al., 2006). Feeding carp with *Astragalus* and *Ganoderma* together can stimulate their respiratory activity and immune response (Yin et al., 2009). Feeding tilapia with *Astragalus* and *Lonicera japonica* can significantly increase blood phagocytosis, reduce mortality after hydrophilic infection, and improve immune response and disease resistance in cultured fish (Ardó et al., 2008). For specific roles, APS can be used directly with other TCM ingredients (Table 1).

## Summary and observations

The immunomodulatory effect of APS is one of the core issues of *Astragalus*-related research. As a TCM feed additive, APS can replace antibiotics, but more research is needed to promote the use of APS in animal production. APS can play an immunomodulatory role by regulating immune organs, immune



cells, immune factors, and certain messenger substances, which have a regulatory effect on both specific and non-specific immunity, and have immunomodulatory functions on both normal and abnormal organisms (Fang, 1994). In terms of tumor immunity APS can be used clinically with traditional therapies for tumors, such as chemotherapy, improving cure

rates and reducing the damage caused by the drugs. In addition, APS as a compound adjuvant also shows a good immune synergistic effect, which provides a valuable supplement for developing new, safe, and efficient immune adjuvants in the future, and has a broad application prospect (Figure 1). With the widespread of COVID-19 worldwide, anti-viral research is even more urgent. TCM plays a massive role in the fight against COVID-19. However, there is less research on the mechanism of TCM for COVID-19, and research should be strengthened in this area to better utilize the role of herbal ingredients in fighting the epidemic.

## Author contributions

By sorting out APS-related literature, the research overview and future trend of APS in immunology were obtained, and the role and mechanism of APS on human immunity were clarified. YL provided research directions and ideas. XW reviewed the literature and wrote the manuscript. RW, ZQ, and YZ participated in the verification and revision of literature. All authors contributed to the article.

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## Conflict of interest

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