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Review Article

Immuno-Potentiating Effects of *Astragalus* Polysaccharides: A Mini-Literature Review

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Abstract

Objective: *Astragalus* polysaccharides (APS) is a promising therapeutic agent because of its long history in ethnopharmacology, extensive research, wide application, and few side effects. Among its diversified properties, APS has been widely investigated for its immuno-potentiating effects such as stimulating T- and B-cell proliferation, regulating the expression of cytokines, activating macrophages, inducing the expression of surface antigens on lymphocytes, and promoting the production of antibodies. **Data Sources:** In this article, we review the research progress of APS focusing on its immuno-potentiating effects. **Results:** Based on the existing studies, APS appears to be a promising adjuvant to anticancer therapy, vaccines, antibiotics, and antiviral therapy. The information provided in this mini-review will provide a useful quick reference for its rational clinical utilization and in planning further research. Further studies are needed to evaluate its dose optimization, mechanism of action, and therapeutic combination strategies. **Conclusion:** APS may be another successful example of the standardization and modernization of Traditional Chinese herbal medicine.

Keywords: Adjuvant anti-tumor, *Astragalus membranaceus*, *Astragalus* polysaccharides, *Astragalus,* cytokines, immunomodulation, immunopotentiation, T-cells

Introduction

Astragalus species has a long history of use in Traditional Chinese medicine.[1] *Astragalus* polysaccharides (APS) is the main active extract of *Astragalus membranaceus* (also known as Radix Astragali or Huangqi). APS is a well-tolerated therapeutic agent and is approved as an injectable Class II Chinese herb.[2] It is comprised polysaccharides, including mannose, D-glucose, D-galactose, xylose, and L-arabinose and glycoproteins.[3] It exhibits a variety of bioactivities including antioxidant, immunomodulatory, anti-tumor, anti-inflammatory, and antiviral activities.[4-6] APS is promising because of its long history in ethnopharmacology, extensive research, wide application, and few side effects.

A few studies have indicated that APS can alter the composition of breast milk, and thus, its use should be avoided in pregnant and nursing women.[7] Tan *et al*. reported in a preclinical study

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that dietary supplementation of APS significantly enhanced the presence of immunoglobulin G (IgG), immunoglobulin M (IgM), epidermal growth factor, and insulin-like growth factor-1 in 0 h-colostrum ($P < 0.001$), and the blocking rates of classical swine fever virus antibody were increased.[8] APS also has galactogog properties;[9] however, no scientifically valid clinical trials support this clinical use. Finally, since dietary supplements do not require extensive premarketing approval from the U. S. Food and Drug Administration and manufacturers do not need to strictly prove the safety and effectiveness of dietary supplements before they are marketed, such dietary supplements may contain multiple ingredients, and differences are often found between labeled and actual ingredients or their amounts.[10] This warrants caution with regard to its use in pregnant and nursing women.

Among its diverse properties, APS has been widely investigated for its immuno-potentiating effects such as stimulating T- and B-cell proliferation, regulating the expression of cytokines, activating macrophages, inducing the expression of surface antigens on lymphocytes, and promoting the production of antibodies.[11] In this article, we review the research progress of APS, focusing on its immuno-potentiating effects. This information will provide a useful reference for its rational clinical utilization and in planning further research.

Cytokine Expression

The immuno-potentiating effects of APS are largely attributable to regulating the production of cytokines. APS upregulates the production of cytokines interleukin (IL)-1α, IL-1 β, IL-2, IL-3, IL-6, tissue necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), fas ligand (FasL) and GrB, immunoglobulins including IgM, IgG, immunoglobulin A, and growth factors including granulocyte monocyte colony-stimulating factor. This APS-induced upregulation has been shown to be dose-dependent for cytokines IL-1 β, TNF-α, and lysozyme-C.[12] It has been shown to inhibit CD4+ CD25+ Foxp3+ T regulatory (Treg) cells in liver cancer patients,[13] IL-10, stromal cell-derived factor 1 in human hepatocellular carcinoma (HCC) cells, and immunoglobulin IgE. Overall, APS can restore the cytokine balance in the tumor microenvironment. It has also been shown to have synergistic anti-tumor effects with doxorubicin in inducing cell death in HL-60 cells.[14] Further, by modulating cytokine release, APS has been shown to inhibit tumor cell growth in Kunming mice with Ehrlich's ascites carcinoma,[15] in rats with gastric cancer,[6] improve the activity of intraepithelial γδT cells in tumor-bearing mice,[16] and to have a synergistic anti-tumor effect with chemotherapy.[1] Owing to its cytokine modulating properties, APS has been shown in preclinical studies (*in vivo* and *in vitro*) to inhibit viral replication, act as an adjuvant to anti-viral vaccines, and enhance the immune response in liver inflammatory conditions such as chronic hepatitis, cirrhosis, and liver cancer.[17]

Cancer-related fatigue

Astragalus polysaccharide (PG2) injection is an approved drug in Taiwan for cancer-related fatigue (CRF). CRF has been reported to be the most frequent and debilitating symptom in 60%–90% of cancer patients. It is a systemic disease, potentially resulting from many underlying mechanisms. Further fatigue and depression may co-exist and show an overlap of symptoms. The impact of APS on cytokine profile and thereby CRF is still under investigation.

Yeh and Wang reported that *in vivo* injections of *A. membranaceus* can suppress the proliferation and differentiation of autoreactive T-cells by elevating Treg IL-10 and reducing IL-6.[18] It has also been shown to further regulate the effects of Thl/Th2 imbalance and secreted cytokines as well as promote the phenotypic and functional maturation of dendritic cells. In another study, APS was reported to regulate the inflammatory response by reducing TNFα secretion in Caco2 cells.[19] However, high dose APS may increase the Th17 cell population, which is known to promote the production and secretion of proinflammatory cytokines.[20] This is an interesting finding, and further studies are required to clarify the mechanism of APS in relieving CRF. Another example of the dose-dependent contradictory effect of APS was observed in a study by Chen *et al*. which evaluated the impact of different doses of APS on the functional status and phenotype of T-cells during polymicrobial sepsis. They observed that lower doses of APS (100 or 200 mg/kg body weight) downregulated the percentages of circulating Th2 cells and Treg cells, and that the percentage of Th17 cells in blood was upregulated in the group receiving a high dose of APS of 400 mg/kg body weight.

Clinically, APS has also been proven to be a complementary and palliative medicine for treating CRF. In a randomized, double-blind, placebo-controlled trial, PG2 administration resulted in greater improvements in fatigue-improvement response rates, enhanced mood, and enjoyment of life for cancer patients. Therefore, PG2 is the first fatigue modulator to relieve fatigue-related psychosocial distress with minimal adverse risks compared with normal saline injections. Among the varied mix of cancer patients included in the study, breast cancer patients benefitted the most from PG2 treatment.[21] Wang *et al*.[22] conducted the first large-scale randomized clinical trial to study the efficacy and safety of pharmacological treatment for CRF with over 300 advanced cancer patients enrolled. They demonstrated that PG2 injection could effectively relieve fatigue in advanced cancer patients.

Regulating Gene Expression in Tumor Cells

APS has been shown to inhibit the gene expression of notch1 and notch3 in nonsmall-cell lung cancer (NSCLC),[23] CD44 in mice with Lewis lung carcinoma,[24] p65, p50, NF-κB, CyclinD1 and Bcl-xL protein in A549 and NCI-H358 cells,[25] FOXP3 in human HCC cells,[11] the NF-κ B pathway in porcine circovirus type 2 (PCV2)[26] and multi-drug-resistant 1 mRNA, Bcl-2 and P-glycoprotein (MRP1)-efflux pump in H22/ADM

hepatoma cells.[27] Gene upregulating effects of APS have been reported in p53, p21, p16, Bax, and caspase-8 of NSCLC,[23] in p53 and PTEN of breast cancer cell line MDA-MB-468,[28] and in Bax/Bcl-2 ratio and caspase of nasopharyngeal carcinoma cell lines,[29] xenograft model and hepatoma cells. APS has been shown to regulate pathways such as p53/murine double minute 2 positive and negative feedback loops in MDA-MB-468 breast cancer cells,[28] Toll-like receptor 4 (TLR4)-mediated MyD88-dependent signaling pathway in macrophage RAW 264.7 and EAC tumor-bearing mice[30] owing to these mechanisms, APS has dose-dependent anti-proliferative and apoptotic effects on tumors and exhibits chemosensitization effects. Wu *et al*.[25] were the first to report the antitumor activity of APS in human NSCLC cells independently of the immunomodulatory effects.

There are some clinical data to support the efficacy and safety of APS in various malignancies. Duan and Wang observed the effect of intravenous APS on enhancing chemotherapy and reducing the toxicity in 120 patients with various malignant tumors. The treated group had a lower progressive incidence, lesser decrease in peripheral white blood cell, and platelet count ($P < 0.05$), accompanied with a significant decrease in CD8 ($P < 0.05$), significant increase in CD4/CD8 ratio ($P < 0.01$), and significant increases in IgG and IgM levels ($P < 0.05$) and Karnofsky scores elevated compared to the control group.[31] Another meta-analysis of 22 studies including 1409 patients indicated that the combination of Astragalus-based Chinese medicines and chemotherapy may increase the efficiency of tumor response rate for the treatment of colorectal cancer patients, improve their life quality based on Karnofsky Performance Status (KPS), and reduce adverse reactions including neutropenia, anemia, thrombocytopenia, nausea, vomiting, and neurotoxicity. Another meta-analysis from Wang *et al*. showed that Astragalus-containing Chinese herbal formulae plus platinum-based chemotherapy was more effective than platinum-based chemotherapy alone in patients with NSCLC.[32] These findings were further validated by Cao *et al*.[33]

Dendritic Cells and T Cell Polarization

APS induces the differentiation and maturation of dendritic cells (DCs) and enhances their antigen-presenting ability.[34,35] Similarly, *in vitro* studies have shown that APS induces the differentiation of splenic DCs to IL-12-producing $CD11c^{high}CD45RB^{low}$DCs, and further mediates the activation of immune function of $CD4^+$ T-cells with shifting of Th2 to Th1.[24] It is noteworthy that this effect was not associated with the inhibition of IL-10 production in CD11c (low) CD45RB (high) DCs. APS has been shown to inhibit Th2 polarization, enhance the gene expression of Th1 cytokines (IFN-γ and IL-2) and its transcript factor (T-bet) and reduce those of Th2 cytokines, and increase CD4(+)/CD8(+) T cell ratio in lung cancer[36] and *Aeromonas hydrophila*-infected mice.[37] Thus, APS reverses Th2 polarization-induced immunosuppression and has potential clinical application in conditions with an imbalance in Th1/Th2 cytokine ratios such as tumors, thermal injury, and bacterial infections.

Natural Killer Cell

Natural killer cells (NK cells) are an important component in the antiviral immune response and are typically activated in response to IL-2, IL-12, IL-15, IL-18, and CCL5. After being treated with APS 15 mg/ml for 48 h, the cytotoxicity of NK cells against leukemic cell line HL-60 cells was shown to be enhanced at different effect-to-target, and the gene and protein expressions in major histocompatibility complex (MHC) Class I chain-related HL-60 cells were upregulated.[38] A study conducted in 1992 by Zhao[39] evaluating the effects of *A. membranaceus* and *Tripterygium hypoglancum* on NK cell activity of peripheral blood mononuclear cells in patients with systemic lupus erythematosus showed that preincubation with

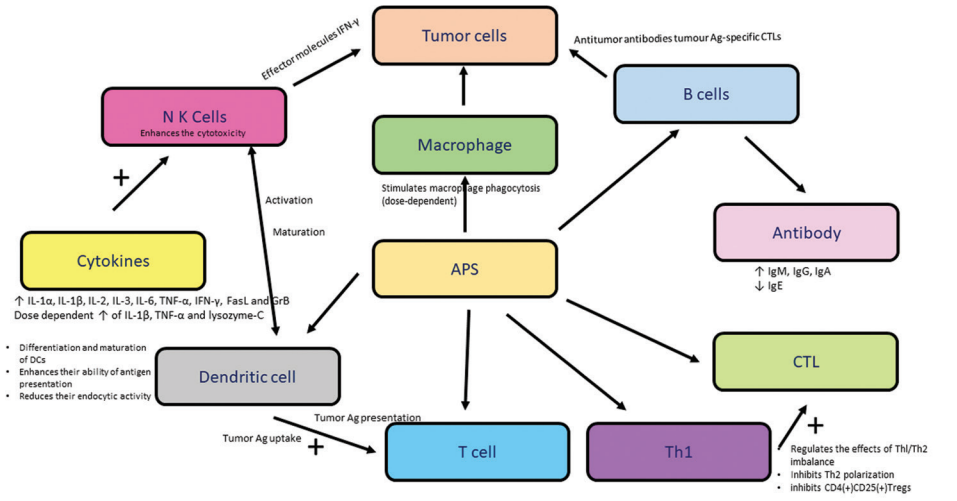

Figure adapted from Zeng P., Li, J., Chen, Y., Zhang, L., 2019. The structures and biological functions ofpolysaccharides from traditional Chinese herbs. Prog. Mol. Biol. Transl. Sci. 163,423–444.

Figure 1: Pathways and activated downstream proteins or cells affected by *Astragalus* polysaccharides

APS considerably stimulated NK cytotoxicity both in systemic lupus erythematosus patients and healthy donors. However, no recent study has evaluated this combination.

T Regulatory Cells

APS has been shown to bind to TLR4 on Tregs, decrease the expression of Foxp3, inhibit CD4(+) CD25(+) Tregs, and resolve infection-induced immunosuppression in burned mice with *Pseudomonas aeruginosa* infection.[40] Indeed, anti-TLR4 antibodies can block the effect of APS on Treg cell immune function. However, high-dose APS (400 mg APS/kg) may excessively repress Treg response and cause excessive polarization toward the proinflammatory Th1 and Th17 lineages and may aggravate sepsis-induced organ injury.[20,41] At a dose of 100 and 200 mg APS/kg, APS has been shown to reduce the number of Treg cells, elicit a balanced Th1/Th2 response, and further attenuate immunosuppression in polymicrobial sepsis.[30] Hence, dose optimization is warranted.

Macrophages

APS stimulates macrophage activity by triggering TLR4-mediated signaling pathways which upregulate the expressions of p-p38, p-ERK, and p-JNK, induce IκB-α degradation and NF-κB translocation, then finally enhance the production of TNF-α, IL-6, and nitric oxide.[42] Hence, APS has high clinical potential in the management of infection caused by bacteria, including *Mycobacterium tuberculosis,*[43] viruses, or fungi such as *Candida albicans*.[42,44] APS demonstrates an interesting dose-response relationship with macrophage phagocytotic activity, wherein phagocytosis is initially enhanced, but with further increases in the dose, high levels of cytokines are produced which downregulates phagocytic function.[43] This again implies the need for dose-optimization studies, particularly in sepsis.

Toll-Like Receptors

APS can induce the TLR4 expression in bladder epithelial cells *in vivo* and *in vitro,*[45] thereby enhancing innate immune response. This finding establishes the use of APS as an alternative option for urinary tract infection treatment. Similarly, APS has been shown to increase immune organ indexes through the activation of the TLR4-mediated MyD88-dependent signaling pathway,[30] thereby reducing tumor weight in EAC breast tumor-bearing mice. However, APS has also been shown to activate B-lymphocytes through membrane Ig in a TLR4-independent manner.[42]

Potential Immune Adjuvant to Vaccines

APS as an adjuvant has been shown to improve the immunogenicity of hepatitis B virus subunit vaccines through humoral and cellular immune responses, affect the TLR4 signaling pathway, inhibit negative regulators such as transforming growth factor-beta (TGF-β) and Treg cells, produce a high level of cytotoxic T lymphocyte (CTL) response and increase IFN-γ production in CD8+ T cells and IFN-γ, IL-2, and production in CD4+ T-cells, and upregulate the expressions of, Gra B, FasL, and Fas in $CD8^+$ T cells.[17] It has also been shown to lead to the dose-dependent upregulation of serum anti-IBV antibody titers in response to IBV vaccination. In an *in vivo* model of immunization with foot-and-mouth disease virus vaccine, APS could upregulate both cellular and humoral immune responses.[46] Similarly, APS could resist the immunosuppression in a chicken model induced with cyclophosphamide by promoting T-lymphocyte proliferation and raising the serum levels of antibody titers.[47] Moreover, in chickens infected with Newcastle disease, APS liposome was shown to promote lymphocyte proliferation and enhance antibody titers.[48] APS may also have the potential to be an effective component in vaccines against classical swine fever virus (CSFV)[49] by inhibiting increases in TF, TGF-β, and IL-8 and inhibiting the upregulation of TLR4 in porcine endothelial cells caused by CSFV.

General Anti-Oxidant Effects

APS reduces reactive oxygen species and endoplasmic reticulum stress, and thus exhibits antioxidant activity. This function has been observed in PCV2 infection *in vitro*[50] and *A. hydrophila*-infected mice[37] *in vivo*. Related to this, an improvement in the quality of life has been observed with APS administration in patients with advanced NSCLC,[51] respiratory system tumors, and gastric tumors.[52] Further, in patients with advanced NSCLC, APS injection with vinorelbine and cisplatin has been shown to reduce fatigue, nausea, vomiting, pain, and loss of appetite.[51] Similar benefits have been achieved in combination with radiotherapy in esophageal cancer.[53]

A summary of the immune-potentiating effects of APS is depicted in Figures 1 and 2.

Conclusion

Based on the existing studies, APS appears to be a promising adjuvant to anti-cancer therapy, vaccines, antibiotics, and anti-viral therapy. It may be another successful example of the standardization and modernization of traditional Chinese herbal medicine. Further studies are needed to evaluate the dose optimization, mechanism of action, and therapeutic combination strategies. Caution must be taken in patients who are on immunosuppressive drugs, in pregnant and nursing women, and in patients with immune system disorders.

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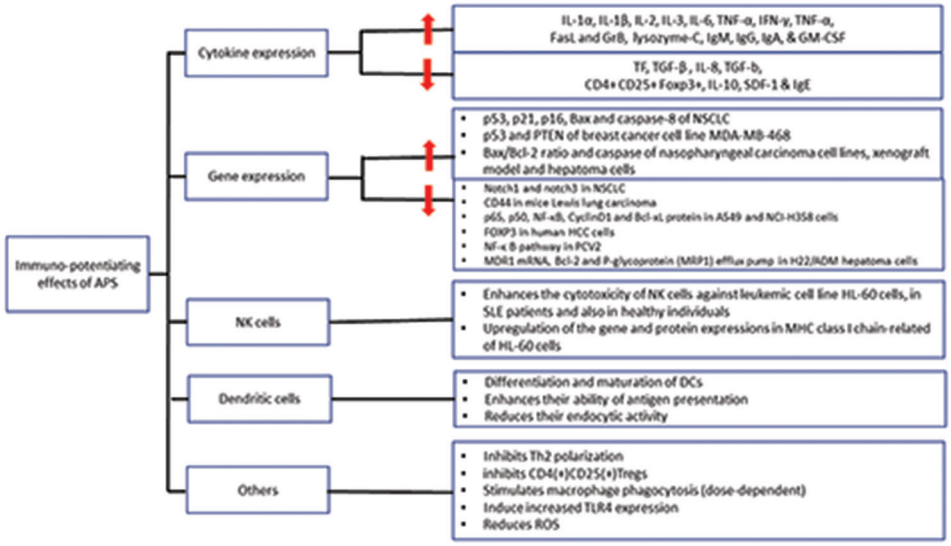

Figure 2: Summary of the immuno-potentiating effects of *Astragalus* polysaccharides

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Conflicts of interest

There are no conflicts of interest.

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