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Health Benefits of *Astragalus Polysaccharides* and Possible Techniques for Upgrading Their Efficiency; A Comprehensive Review

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Abstract

Astragalus polysaccharides (APs) are hydrophilic heteropolysaccharides derived from the stalks or roots of *Astragalus membranaceus*, a Leguminosaceae plant. It is commonly known in Chinese as Huangqi or Radix Astragali. The main active component of *Astragalus membranaceus* is the APs, which possess a number of pharmacological properties as well as contributing to the efficacy of drugs. The structure of Aps is composed of flavonoids, saponins, alkaloids, and polymeric carbohydrates that are joined by alpha-type glycosidic unions. It is now possible to treat a wide variety of diseases with APs, including cancer, cardiovascular disease, diabetes, and neurological disorders. A substantial number of in vitro and animal studies have clarified the treatment procedures and effects of APs on a variety of disorders. There is a limited therapeutic potential for APs. Due to their bulkiness, restricted solubility, and negatively charged properties, APs have limited therapeutic potential due to their low bioavailability and large molecular weight. Our review summarizes the pharmacological actions of APs as well as provides research investigations and major clinical information that will help widen clinical outcomes by elucidating treatment methods. Moreover, the review presents the approaches to improve the bioavailability of APs in the future by altering their structure and transforming them into nano-forms.

Keywords: *Astragalus membranaceus*, *Astragalus* polysaccharides, virus, bacteria, parasite and pharmacodynamic characteristics.

1. Introduction

Herbal medicine is now a significant complementary or alternative method of drug administration. Today, complementary or alternative drug delivery mechanisms increasingly rely on traditional medicine. There is a comprehensive philosophy underlying traditional Chinese medicine [1]. Therapies based on traditional medicine principles are holistic [2]. In over 2000 years of use, *Astragalus membranaceus* (AM) and Astragali Radix have been used as herbal medicines [3, 4].

Astragalus membranaceus is an ancient Chinese herb with a long clinical history that is abbreviated AM. In addition to polysaccharides, flavonoids, saponins, and alkaloids, AM also contains flavonoids and saponins [1]. Astragalus is effective in enhancing immune system response, avoiding upper respiratory infections, dropping blood pressure, and controlling diabetes. Astragalus was found to exhibit antibacterial and anti-inflammatory properties [2]. AM has recently been used to treat fever, poor appetite, anemia, wounds, and uterine prolapse [3]. AM contains around 200 components such as isoflavonoids, amino acids, saponins, and polysaccharides [4]. AM is characterized by a straight, long, cylindrical root that is 20-50 cm long and 50-150 cm tall makes up the plant [5].

It has been established that the therapeutic effects of AM are attributed to its polysaccharide constituent. *Astragalus* polysaccharides (APs) are considered vital macromolecule of AM that exhibits potential biological activity including antioxidant, anti-inflammatory, diabetic, anticancer, and immunomodulatory properties [6, 7]. Moreover, APs are characterized by low toxicity, minimal side effects, low residues, and non-tolerance [8, 9].

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Antibiotics frequently lose their strength over time due to the formation of drug resistance in bacterial infections, resulting in the incidence of an "antibiotic resistance crisis" [10]. Due to the prospective promising future substitutional role of the AM and its valuable components. *Astragalus membranaceus* might be considered a powerful safe natural antimicrobial agent [11, 12].

The bioavailability of APs was found to be limited after oral administration due to its low solubility [13]. Different mechanisms have been used to improve the bioavailability of such macromolecules involving utilizing nanoparticles or applying delivery systems for such macro-molecules [14]. Similarly, structure modification of APs by chemical, enzymatic, or physical methods could enhance the pharmacological effects of APs in the future [15]. This review emphasizes the most current achievements in research on *Astragalus* polysaccharide therapeutic pathways and pharmaceutics to provide experimental research underpinnings as well as possible ways to improve its bioavailability.

2. Extraction, preparation, and Structural features of Aps

The chemical structure of AM consists of saponins, flavonoids and polysaccharides are the most biologically active constituents, along with sucrose, phenolic acids, and amino acids. Polysaccharides from *Astragalus* have been the attention of researchers in the last periods due to their therapeutic properties with no side effects [16]. The main APs extraction techniques involve the extraction of water, enzymes, microwaves, and alkali water. Water extraction is considered the best technique to extract polysaccharides. This technique is applied by boiling the water to 100°C for 1 hr each time, the procedure was repeated 3 times. The extraction rate is 3.570% and the ratio of liquid to solid is 1:10 g/ml. The greatest result was achieved when protein is divided with tannic acid [8].

Destruction of AM fiber by alkali facilitated the flow of polysaccharides. In comparison to the warm water method of APs extraction, microwave-assisted extraction required less extractant, took less time, and produced more APs [17]. The enzymes inside the cell wall and membrane can become inactive when exposed to microwaves. This increases the output of polysaccharides and enhances the flow of APs. Similar findings were made for the ultrasonic-assisted separation of APs technique that showed that the extraction rate could reach 92.1% after one hour [18].

The primary element of the outer membrane is cellulose. Cellulase can break down the AM cell wall and increase polysaccharide extraction rates. [19]. In comparison to the water extraction method and the alkali extraction method, the yield from the separation of APs by using the alcohol alkali method was 3.53 times greater and 2.63 times higher, correspondingly [15]. The output of APs when they were extracted with a calcium oxide mixture varied depending on the circumstances. The outcomes demonstrated that when pH was 9.0, the yield and quality of the isolated APs were at their greatest [17].

It is estimated that AM contains up to 100 mg/g of APs. It is possible to identify the structure of a polysaccharide in terms of its molecular weight (MW), arrangement of monosaccharides, and organization and location of glycosidic bonds [23]. As a result of the complex structures of their macromolecules, singular APs are generally difficult to characterize. Polysaccharides were isolated and characterized using HPLC, gel-permeation chromatography, periodate oxidation, partial acid hydrolysis, and nuclear magnetic resonance (NMR).

As a result of the extraction method, APs have different structures. Sugars 94.59 and 97.57 % of APs-I and APs-II are produced through boiling water and alcohol precipitation, respectively, using 30% and 70% ethanol. In a study on mice ascites tumors, 55.47% of APs-I (50 mg/kg) suppressed the tumors, while the effect of APS-II (50 mg/kg) suppressed the tumors by 47.72%. Extracted APs vary in composition and operation depending on temperature, according to recent studies. While glucose is the primary constituent of APs4 and APs90 were isolated at 4°C and 90°C, respectively, and the main chain of both compounds is made up of (1→2) α-D-Glcp, APs4 exhibited a larger amount of (1→2) α-D-Glcp and inhibited MGC-803, A549, as well as HepG2 cells to a greater extent. This suggests that the enhanced in vitro anticancer activity of APs4 may be due to the increased branching degree [24].

Currently, over 30 types of APs have been identified, mostly dextran and heteropolysaccharides [25]. Polysaccharides have a complex chemical structure, which limits our understanding of their exact components. There are different compositions and proportions of monosaccharides in polysaccharides with various molecular weights. As a result, the biological activities that correlate to the different glycosidic bond types and sugar chain connections will likewise vary. APs can be identified by gas chromatography-mass spectrometry using eight different glycosidic bond types. Nuclear magnetic resonance also revealed that anomeric hydrogen has a configuration [26]. The main ingredients of APs are heteropolysaccharides, dextran, neutral polysaccharides, and acidic polysaccharides. Although dextran comes in both hydrophilic and hydrophobic forms [27], heteropolysaccharides [11] are acidic, water-soluble polymers. The root of AM contains an acid heteropolysaccharide with a relative molecular weight of 76 kDa. A small fraction of O-acetyl groups and peptide residues are found in [28], which states

that it is composed of L-arabinose, D-galactose, D-galacturonic acid, and D glucuronic acid (18:18:1:1). APs were also revealed to contain six different types of monosaccharides, including amylaceum, seminose, arabinose, xylose, glucuronic acid, and rhamnose, with relative composition ratios of 12.83: 0.27: 0.71: 1.63: 1.04: 0.56 [29]. Of the 14 types of polysaccharides isolated from *Astragalus*, 13 have β-D (1→6)-galactooligosaccharide branching β -D-(1→3)-galactose [11]. The root of AM included 24 different forms of polysaccharides, the majority of which were heteropolysaccharides. Heteropolysaccharides have a molecular weight that varies from 8.7 to 4,800 kDa and are made up of a variety of monosaccharides, such as L-rhamnose, L-rabinose, D-xylose, L-xylose, D-ribose, L-ribose, D-galactose, D-glucose, and D-mannose [23]. This heteropolysaccharide ranges in molecular weight from 8.7 to 4800 kDa and contains different proportions of 9 monosaccharides, including galactose, glucose, rhamnose, arabinose, xylose, mannose, fructose, fucose, and ribose.

AM contains both water-soluble and insoluble glucans and heteropolysaccharides as polysaccharides. Hot water is used to extract the polysaccharides known as astragalan I, II, and III. Astragalan I is a neutral heteropolysaccharide with a D-glucose, D-galactose, and L-arabinose ratio of 1.75:1.63:1. Its molecular weight is 36 kD. α-(1,4)-glucans were astragalans with molecular weights of 12 kD and 34 kD, respectively [31]. Alcohol precipitation and water extraction were used to separate APS I and APS II. The composition of APs I was 1: 6.25: 17.86 for rhamnose, arabinose, and glucose, while APs II had the same composition in a different ratio of 1: 6.25: 17.86 [32]. It has also been reported that acidic polysaccharides such AH-1, APSID3, and AMem-P exist [30]. Amem-P is a complex acidic polysaccharide with a molecular weight of 60 kD. Its major constituent is hexuronic acid, to which are connected residue groups of α-1,5-linked arabinofuranose, terminal and β-1,3-, β-1,4-, β-1,6-linked, 3,6-branched-D-galactose, and 2,4-branched-L-rhamnose. Astroglucans A, B, and C, as well as additional *Astragalus* polysaccharides AH-2, AE, AEF-1, and AEF-2, have been reported [31]. Additionally, certain glucans from AM with a molecular weight of 12-36 kDa had been identified. The primary identification of these glucans was -(1-4)-d-glucans [33]. Moreover, from industrial waste residue that had been removed via AR, a novel polysaccharide known as AERP was isolated. It was composed of two components, AERP1 and AERP2. In addition, NMR and HPLC analyses were used to determine the structural identity of these components. AERP2 is a glucan with a MW of 2.11 × 103 Da, while AERP1 is an acidic component with a MW of 2.01 × 106 Da. [34].

3. Properties of APs

3.1. Antiviral effects of APs

Potential APs antiviral actions against many viruses are displayed (Figure 1). APs dose-dependently downregulated the mRNA transcription of IL-1β, IL-6, IL-8, and TNF-α in chicken embryo kidney (CEK) cells, demonstrating antiviral activity against infectious bronchitis virus (IBV) at various dosages (1, 5, 10, 20, 30, and 50 μg/ml) [20]. According to earlier studies, APs improved the immune response in young chickens suffering from infectious bursal disease (IBDV), which is characterized by high rates of morbidity and death. The synthesis of erythrocyte-C3b receptor rosettes was significantly enhanced in Haline White chickens when APs were given at 5 and 10 mg doses during a six-day period after the first infection [21].

Furthermore, by reducing oxidative stress and activating the NF-κB signaling pathway, APs were discovered to impede the replication of pig circovirus type 2 (PCV2), which was thought to be the causal agent of swine circovirus-associated illness, in vitro [22]. Additionally, it was noted that APs (5, 10, and 20 mg/kg) may considerably increase the specific antibody titer, interferon (IFN)-γ, and IL-6 mRNA expression of the foot and mouth disease virus (FMDV) [23]. This suggests that APs can protect against FMDV. Moreover, APs have the potential to prevent the herpes virus from proliferating in mice at a dosage of 30 μg/mL [24].

APs, when used as a vaccine adjuvant, increased the phagocytic ability of peritoneal macrophages, the proliferation of splenic lymphocytes, the titer of serum antibodies, and the production of IL-4 and IL-10 at doses of 0.125 and 0.5 mg in BALB/c mice [25]. By inducing CD4+ T cells to produce IL-4, IL-2, and IFN-γ and enhancing CD8+ T cell expression, APs may also improve the effectiveness of the Hepatitis B virus (HBV) vaccine [26]. It was discovered that sulfated modification of APs was more effective in both in vitro and in vivo against duck hepatitis A virus (DHAV) than non-modified APs [27]. Furthermore, sulfated APs significantly reduced the bursal disease virus's (IBDV) infectivity as compared to non-modified APs [28].

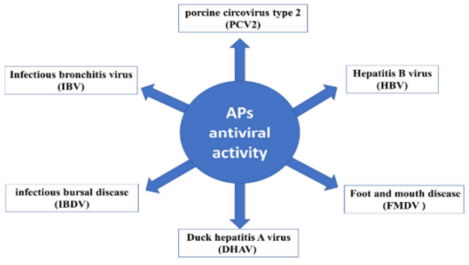

Figure 1: APs have significant antiviral activity against multiple viruses

3.2. Immune enhancer

APs stimulate cytokine expression and promote immunity under normal physiological conditions. However, following a proliferation of cytokines because of an inflammatory response, APs were found to downgrade inflammatory response factors (Table 1). APs of four or eight mg/kg of body weight have been shown to alter chickens' cellular and humoral immune responses when administrated for 21 days. This is achieved by stimulating the formation of lymphocytes (T and B cells), boosting the synthesis of cytokines by stimulating macrophages and B cells and boosting humoral immunity by raising the titers of certain antibodies. Additionally, by increasing the number and/or activity of complement receptors on the membrane of erythrocytes, such as the erythrocyte-C3b immune complex rosette rate, or E-ICRR, and the erythrocyte-C3b receptor rosette rate, or E-C3bRR, APs can improve the immune adherence of erythrocytes in chickens during infection [29].

Piglets were found to benefit from APs (800 mg/kg/day for 28 days) by reducing the immune stress caused by LPs and enhancing intestinal function, which led to accelerated growth [30]. In a similar vein, adding APs to the turbot basal diet at a level of 150 mg/kg per day for 63 days increased both the growth rate and TLR expression [31]. Furthermore, after 40 weeks of daily administration of a diet containing APs (10 g/kg), the level of serum interferon was increased in young chickens [30, 32].

Diets containing APs at a dose of 1.5 g administered one week before the predicted delivery date significantly increased swine fever virus titers in sows and enriched sow colostrum immunoglobulin levels [48]. After six weeks of dietary supplementation, APs (2 g/kg) could improve the immunity of newly born broilers and their growth rate [49]. For two weeks, daily administration of APs (200 mg/kg) enhanced the index of the thymus and spleen, improved the kidney and thymus histology, and increased phagocytosis of peritoneal macrophages in mice [50]. Recombinant protein-heat-shock protein (rP-HSP) vaccinated mice showed significant increases in IgG titers (IgG) and interleukins, such as IL-2, IL-4, and IL-10, following two weeks' administration of APs (100 g) twice daily [51].

Regarding in vitro research, APs (25 μg/mL) treatment of macrophages for 48 hours increased the amount of NF-κB mRNA, suggesting that APs may target the TLR4/NF-κB signaling pathway in macrophages [33]. A further study found that APs (1000 g/mL) for 48 hours inhibited macrophage 4T1 levels by stopping the cell cycle at the G2 phase [33]. After treating DCs with APs solution (125 μg/mL) for 48 hours, there was a significant increase in macrophage phagocytosis in addition to T-cell, IFN-γ, IL-2, CD80, CD86, and bone marrow-derived DC production [34]. Additionally, following a 72-hour APs treatment at a dose of 200 mg/mL, mesenchymal stem cell production rose significantly [35].

3.3. Anti-inflammatory effects of APs

It was discovered in multiple in vitro and in vivo investigations that APs have a significant anti-inflammatory impact. APs (2.5 mg/ml) reduced the expression of ICAM-1, NF-κB p65, and IL-8 in hy926 cells [36]. Moreover, the expression of IL-10 and the macrophage mannose receptor (MMR) was decreased in RAW264.7 cells that had been palmitate-treated for 24 hours when APs were added [37]. Furthermore, in LPS-infected Caco2 cells, APs could effectively block the activation of toll-like receptor 4 (TLR4) [38]. Additionally, in LPS-treated RAW264.7 cells, Aps and honey-processed *Astragalus* polysaccharide (HAPS) decreased the production of TNF-α, IL-1β, IFN-γ, and IL-22 [39]. Likewise, LPS-stimulated THP-1 cells demonstrated that APs had anti-inflammatory properties. A concentration of 50–200 mg/mL of APs inhibited the phosphorylation of ERK and JNK, two key signaling pathways that generate TNF-α and IL-1β, and they also inhibited the expression of NF-κB [39].

APs (200 mg/kg) injected daily for two weeks significantly decreased the colitis caused by salt. This result was explained by APs' capacity to reduce myeloperoxidase and NF-κB activity levels [40]. When APs were given to rats for one week at a dose of (400 mg/kg), the same outcomes were seen. Sulfonic acid-induced colitis was considerably lessened by APs by modifying the amounts of T-cells and IL-17 in intestinal cells [41].

APs, administered daily for two days at a dose of 100 mg/kg, reduced the pulmonary inflammation in mice caused by LPS. Goblet cell metaplasia and NF-κB translocation were also suppressed by APs [42]. Additionally, in rats with chronic obstructive pulmonary disease, APs (200 mg/kg) administered daily for one week changed the expression of TNF-α, IL-6, IL-8, and TNF-α [43].

Moreover, by decreasing the expression of CD34 on the surface of microvascular endothelial cells, APs impeded the adhesion of inflammatory cells to these cells [12]. Furthermore, in rats fed a high-fat diet, APs suppressed the production of TNF-α and NF-κB [44]. Consequently, APs have the ability to affect a multitude of inflammatory pathways and mediators, which may interfere with a range of inflammatory diseases. More investigation is required into the targets of APs' anti-inflammatory action, despite the fact that its molecular and cellular effects have already been examined.

Table (1): effect of APs on cytokines and inflammatory mediators

Molecule	Effect	Study	References
Lymphocyte (T and B cells)	Promote	In vivo In vitro	[29], [34].
IL-1β	Decrease	In vitro	[39].
IL-2	Promote	In vivo In vitro	[45] [34].
IL-4	Promote	In vivo	[45].
IL-10	Promote	In vivo	[45].
IL-12	Promote	In vivo	[46].
IL-17	Decrease	In vivo	[41]
IL-22	Decrease	In vitro	[39].
IFN-γ	Promote	In vitro	[34].
CD80	Promote	In vitro	[34].
CD86	Promote	In vitro	[34].
IL-8	Decrease	In vitro	[36]
NF-κB	Decrease	In vivo In vitro	[40]. [36]
p65	Decrease	In vitro	[36]
ICAM-1	Decrease	In vitro	[36]
TNF-α	Decrease	In vivo In vitro	[43], [39].

3.4. Anti-bacterial effects of APs

APs' antimicrobial activity is encouraging [29]. APs showed a dose-dependent bacteriostatic effect when applied to harmful bacteria, such as Streptococcus, Escherichia coli (E. coli), and Staphylococcus aureus (S. aureus). Green silver nanoparticles (AgNPs) were synthesized using a water-soluble fraction of polysaccharides isolated from AM roots (AMWP) [47]. When applied to clinically isolated multidrug-resistant bacteria (Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-resistant *Staphylococcus epidermidis* (MRSE), E. coli, and *Pseudomonas aeruginosa* (*P. aeruginosa*)) and relative reference strains (S. aureus ATCC 29213, *S. epidermidis* ATCC 12228, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 15442), the synthesized AMWP-AgNPs exhibited notable antibacterial activity at relatively low concentrations (minimum inhibition concentrations, or MICs) ranging from 0.032 to 0.063 mg/mL). Particularly, there was a notable decrease in the multidrug-resistant bacteria.

APs increased the expression of human cathelicidin antimicrobial peptide (LL37), a crucial host anti-infective molecule, in respiratory epithelial cells HBE16 and A549, both at the mRNA and protein levels. Furthermore, the LL-37 monoclonal antibody partially neutralized the evident antibacterial activity of the lysate and supernatant from APs-treated HBE16 cells. Moreover, APs led to the degradation of IκBα and markedly increased the phosphorylation of JNK and p38 mitogen-activated protein kinase (MAPK). APs-induced LL-37 production and antibacterial activity were decreased by specific inhibitors of p38 MAPK, JNK, or nuclear factor-κB (NF-κB), respectively. When combined, APs increase pulmonary epithelial cells' LL-37 induction and antibacterial activity, which may be because they activate the p38 MAPK/JNK and NF-κB pathways. The clinical utility of APs in the treatment of infectious diseases was further validated by these results [48].

There is a lot of fiber and carbohydrates in *Astragalus* that can ferment and produce short-chain fatty acids. Fecal microorganism composition was enhanced after a 21-day exposure to 0.5% crude AM added to the laying hen diet. Because of this, it is good for you and helps to control the microbiota in your feces [49].

The microbial populations were significantly affected when ill chickens naturally infected with avian *Mycoplasma gallisepticum* were fed AM extract at a concentration of 2 g/kg. Following a one-week treatment period, the extract induced growth in chickens and led to a rise in lactobacilli and bifidobacteria, which are possibly beneficial bacteria, and a decrease in E. coli and other potentially harmful bacteria (Bacteroides spp.). Thus, in sick chickens, this plant polysaccharide extract showed some promise as a possible modulator of intestinal microbiota [50].

Lactobacilli and Bacillus cereus counts significantly increased in chicks supplemented with 220 mg of APs per kg of diet, although E. coli numbers fell. Given that they may function as prebiotics, APs seem like a viable substitute for probiotic use [51].

3.5. Anti-parasitic effects of APs

Although APs have potential bioactivity as immunity-enhancing, antioxidant, antiviral, anti-microbial, and anti-parasitic agents, few studies have reported on the antiparasitic effect of APs [29]. It was discovered that APs functioned as an adjuvant for the immune response triggered by UV-attenuated *Toxoplasma gondii* in animal models [52]. Furthermore, studies using 24-well tissue culture plates with 500 µL of filtered seawater (30% salinity) and 500 µL test solutions in each well showed that APs were effective antiparasitic agents against the Fish Monogenean *Neobenedenia girellae* [53]. These experiments produced final concentrations of 1,001, 500, 250, 125, 62.5, and 31.3 mg/L. Additionally, in male Wistar rats weighing 250–300 g, APs reduced the development of Trypanosoma cruzi when administered at a final dose of 250 µg/ml. Additionally, in male Wistar rats weighing 250–300 g, APs reduced the development of *Trypanosoma cruzi* when administered at a final dose of 250 µg/ml [54]. Additionally, APs had a significant impact on the humoral and cellular immune responses of chickens infected with *Eimeria tenella*. Different combinations of extracts were fed to the birds for a week (from eight to fourteen days of age). It was believed that giving the supplement at a level of 1 g/kg of the diet would

be the best way to improve the health of the hens [3]. Similarly, in in vitro and in vivo experiments using male Swiss albino mice weighing 22–25 g, where the mice were divided into five groups of eight mice each, APs inhibited the Eimeria oocyst sporulation. Four of the group contracted Eimeria, while the first group remained uninfected. One hour after infection, APs were administered to the third, fourth, and fifth groups at dosages of 10, 25, and 50 mg/kg, respectively [55]. In vivo and in vitro, anti-*Toxoplasma* actions are exhibited by APs. Moreover, APs were introduced to the wells containing *T. gondii*. 200 l of RPMI 1640-supplemented media and APs (10 mg/ml) concentrations were present in each well of a 96-well culture plate [10]. A recent study found that APs may be an herbal antibacterial and anticoccidial medication that reduces infection in chickens. For 1, 3, 6, 9, 12, 24, and 36 hours, Eimeria oocysts were exposed to 10, 25, and 50 mg/ 5ml of APs [56]. These results suggest that antipsychotic medications (APs) have played a critical role in the treatment of a number of diseases brought on by protozoal parasites, such as *amoebiasis, intestinal coccidiosis, giardiasis, leishmaniasis, toxoplasmosis, trypanosoma* (which causes sleeping sickness and Chagas disease), and *trichomoniasis* [54]. Numerous research teams are searching for antiparasitic medications that are both low-risk and effective. Here, we outline the most recent developments for natural antiparasitic medications [57, 58].

3.6. Antidiabetic effect of APs

In several in vivo studies, APs were used to treat type 2 diabetes mellitus and lower blood sugar levels. APs at a dose of (100 mg/kg) daily for 8 weeks significantly reduced serum fasting plasma glucose, hemoglobin A1c, and insulin levels in a diabetic mouse model via the TGF-/caspases pathway compared to streptozotocin-induced diabetic rats [59]. Similarly, in an HFD-induced insulin resistance mouse model, APs at 800 mg/kg daily for 12 weeks reduced lipid and blood glucose levels significantly more than metformin [60]. Furthermore, APs (500 mg/kg/day for 8 weeks) increased the expression of miRNA-203a-3p, which regulates glucose-regulated protein 78 (GRP 78), resulting in decreased insulin resistance in diabetic rats [59]. The pathophysiology of diabetic cardiomyopathy (DCM) has been linked to oxidative stress and apoptosis. Oxidative stress in cardiac myocytes was identified as a key etiology of DCM. In diabetic mice with heart failure, treatment with APs solution (800 g/mL for 24 h) reduced the proliferation of pro-apoptotic proteins and managed the protein expression of oxidizing target genes, indicating that APs can reduce oxidative stress and diabetic cardiomyopathy damage [36]. APs induced similar improvements in mice with diabetes-induced memory loss. Fasting plasma glucose, insulin, and hemoglobin A1c levels in mice were reduced after 8 weeks of treatment with APs at a dose of (800 mg/kg/day). The mechanism may be related to the effects of APs on lipid metabolism, glucose, antioxidation, and infrared radiation [61].

Concerning *in vitro* studies, APs were found to act in a similar pathway of metformin through controlling phosphorylation cascades that are stimulated by insulin in the HepG2/IR cell model. Particularly, APs dramatically modulated autophagy and pro-apoptotic endoplasmic reticulum (ER) stress responses, signifying their support of cell persistence [60]. Moreover, APs (100 μg/mL) over 48 hours preserved mitochondria, initiation of antioxidant enzyme activity, and inhibition of cellular ROS production in H9C2 cells subjected to elevated glucose [62]. In 3T3-L1 preadipocytes, AMPK activation improved insulin sensitivity and increased the uptake of glucose. There was an increase in the concentration of phosphorylated AMPK following APs therapy (10 g/mL for 48 hours) [48]. Furthermore, APs solution (100 g/mL) for 2 days stimulated the neuregulin 1 (NRG1) expression in the DCM cell model that might augment cardiac muscle cell proliferation and diminish apoptosis [63]. Besides, A 72-hour preliminary therapy with an APs solution (50 μg/mL) protected against diabetic retinopathy, a severe complication of diabetes mellitus, through reversing miR-204 expression, causing disinhibition of SIRT1 and reduced apoptosis induced by ER stress through downregulating the apoptotic markers [64].

3.7. APs' effects on neurological disorders

The brain's hippocampus is the source of neural stem cells (NSCs) that can self-renew and differentiate into multiple lineages [65]. The importance of oxygen in regulating NSC development and differentiation is well established [66]. NSCs may be subjected to hypoxia that reduces cell viability and leads to cell death. MicroRNAs (miRNAs), which are intrinsic non-coding RNAs, induce gene expression after transcription by binding to and destroying target mRNAs' untranslated regions [67]. MiR-138 has been shown to defend cells against hypoxia-induced apoptosis [68]. APs (5000 μg/mL for 2 h) were found to protect NSCs from hypoxia by stimulating the production of miR-138 and blocking P38MAPK and JNK pathways. Further, Aps upregulated the anti-apoptotic markers such as caspase-3, caspase-9, and BAX, while inhibiting the production of apoptotic markers such as Bcl-2 [69].

The most commonly used approach when assessing sclerosis is experimental autoimmune encephalomyelitis (EAE) induced by MOG35–55 [62]. The expression of MOG35–55-specific T cells was inhibited by 500 mg/kg of APs daily for one week as a preliminary treatment and the proliferation of

proinflammatory cytokines was markedly reduced [70].

Moreover, the buildup of abnormal protein-induced impairment of cellular hemostasis causes several neurodegenerative diseases such as Huntington's disease (HD), Parkinson's disease, and Alzheimer's disease [71]. APs were found to hinder the accumulation of the abnormal polyglutamine (polyQ) in Caenorhabditis elegans, which induces HD, via regulation of DAF (abnormal dauer formation)-16/FOXO (forkhead box O) transcription factor [72].

Overaction of microglia produced several neurotoxic factors including reactive oxygen species, nitric oxide (NO), and prostaglandin E2 (PGE2) [4]. Treatment of BV2 microglial cells with 200 µg/mL of APs solution for 1 hour before the stimulation with lipopolysaccharide, the translocation of translocation of NF-κB was repressed. Moreover, PGE2, NO, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) activities were diminished [4]. Further, overactivation of microglia and/or astrocytes and abnormalities in brain insulin signals could induce sporadic Alzheimer's disease. Insulin resistance diminished after seven weeks of oral APs solution treatment at a concentration of 500 mg/kg every 12 hours as well and the activity of astrogliosis and microglia was suppressed in high-fat diet mice [73].

3.8. Cardiovascular disorders and the effects of APs

APs were found to treat several cardiovascular disorders. Administration of APs (200mg/kg) daily for 2 weeks prevents myocarditis induced by coxsackievirus B3 by controlling the toll-like receptor (TLR)-4/NF-κB p65 pathway. Besides, APs markedly reduced the production of inflammatory cytokines within heart tissues resulting in restriction of tissue damage [74]. In H9c2 cardiomyoblasts, APs reduced damage induced by LPS through enhancement of cell survival, decreasing apoptosis, and impairing inflammatory markers release. Toll-like receptor 4 (TLR4) expression was likewise elevated in LPS-treated H9c2 cells by APs. Furthermore, APs protected LPS-treated H9c2 by reducing miR-127, NF-κB, and JNK expression. Besides, APs promoted phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathways [75].

APs administered at a dose of (750 mg/kg/day) for 8 weeks reduced the volume of hypertrophied myocardium and lowered cardiomyocyte death in rats via raising Bcl-2 protein expression and lowering caspase-3 and Bax protein levels [76]. Besides, APs solution (50 µg/mL for 48 hours) was reported to regain the usual autophagic flux of myocytes as well as diminish doxorubicin-induced cardiotoxicity in C57BL/6J mouse by regulating the AMPK/mTOR pathway [77].

On the level of endothelial function, daily intragastrical treatment with APs at concentrations of 400 and 800 mg/kg for two weeks diminished vascular endothelial impairment and hypertrophy induced by isopropanol in rats. Further, APs declined ROS, p65, TNF-α, and IL-6 concentrations; whereas upsurged the expression of cGMP in the aortas was considered as a marker for nitric oxide [78]. Similarly, APs (100 g/mL) administration for 1 hour diminished H2O2 production, which caused impairment in human umbilical vein endothelial cells (HUVEC) through successful restoration of mitochondrial membrane potential [79]. These findings demonstrate how APs might represent a promising drug used to treat multiple cardiac diseases.

3.9. Anti-cancer effects of APs

APs have anti-tumor actions as well as increase the effectiveness of chemotherapeutic drugs, reduce tumor cell growth, and induce cell death. Moreover, APs play a part in the capability of the immune system to combat tumors. One of the most effective therapies for metastatic and highly aggressive cancer was chemotherapy. On the other hand, the toxicity of chemotherapy medications at large doses made their long-term clinical use impossible. The confirmed chemotherapy-sensitizing effects of APs on cancer would increase the effectiveness of chemotherapy drugs [80, 81].

Several in vitro researches have reported the anti-cancer effect of APs. The combination of apatinib (20 µg/mL), a medicine for gastric cancer, and APs (200 µg/mL for 24 h) reduced the proliferation, migration, and invasion of gastric tumor AGS cells via decreasing matrix metallopeptidase 9 (MMP-9) and phosphorylated AKT production [80]. In cells from non-small cell lung cancer, co-administration of 10-hydroxy camptothecin and APs solution for 24 hours at a concentration of (1000 g/mL) increased cell autophagy while regulated mitogen-activated protein kinase 3 (MAP4K3)/and mTOR signaling pathway resulting in a more potent anti-tumour impact [82].

Besides, co-administration of APs solution (800 µg/mL) for 72 hours enhanced the antagonistic effect of cisplatin (10 µg/mL) on the survival of ovarian cancer SKOV3 cells via stimulating the JNK1/2 signaling system [83]. In the meantime, APs (0, 1, 5, 10, 20, 40 mg/ml) and at various periods (0, 24, 48, 72, 96 h) controlled the expression of miR-138-5p, which decreased the expression of SIRT1 in human prostate cancer cells (PC3 and DU145) in a dosage and time-dependent way [3]. In ovarian cancer cells, APs (2000 µg/mL for 24 hours) solution inhibits the PIK3CG/AKT/Bcl-2 pathway that greatly suppresses

tumor cell activity in triple-negative breast cancer and encourages apoptosis [84].

Human osteosarcoma MG63 cells were prevented from survival, proliferation, or penetration via APs (20 mg/mL) which increased miR-133a expression. Further evidence that APs functioned as an anti-osteosarcoma agent by stimulating miR-133a besides deactivating the JNK pathway was provided by the fact that cutting down miR-133a restored the inactivation of the JNK pathway produced by APs (10 mg/kg for 24 h) [85]. APs (400 mg/kg/day for 15 days) inhibited the development of hepatocellular carcinoma (H22) cells by 59.01%. The spleen and thymus indices had higher IL-2 and TNF-α concentrations, showing that APs changed the immune system's capacity to regulate anticancer activity [86].

Similar to how APs solution (1000 µg/mL for 24 h) did not affect MCF-7 cell growth, APs-activated RAW264.7 macrophages inhibited tumor cell proliferation by generating NO and TNF-α and stopping the cell cycle in the G1 phase [87]. APs influenced macrophage function in mediating additional anti-tumor action, according to a new tumor model created using tissue engineering that may accelerate the development and proliferation of tumor spheroids. APs-treated RAW 246.7 macrophage lowered tumor size, increased the fraction of apoptotic cells, and decreased human breast cancer cell growth. APs solution (1000 µg/mL for 72 hours) killed H22 cells via decreasing Notch1 expression [88]. The APs solution (300 g/mL for 24 h) stimulated macrophage polarisation to the M1 phenotype through the Notch signalling system, thereby enhancing anti-tumor actions and inhibiting tumor progression. When APs-induced macrophages were implanted with 4T1 tumor cells, the tumor volume and weight in BALB/c mice were decreased [89]. APs alone had little effect on the 4T1 cells, but they did augment the cytotoxic effects of RAW264.7 cell supernatant on these cells. APs solution (300 µg/mL for 24 h) increased TNF-α, IL-6, and iNOS production via TLR4-mediated activation of MAPKs and NF-B [90].

Additionally, conventional therapy for advanced squamous cell carcinoma of the head and neck has severe side effects including pain and appetite loss. Patients who received APs (500 mL) daily diminished the side effects following receiving the medication three times per week for 2 months [91].

Prostate cancer invasion and proliferation were found to be significantly reduced by APs. A recent study found a connection between a high-cholesterol diet and prostate cancer (PC) progression [92]. APs (100 mg/kg) were found to suppress cell proliferation as well as reduce the levels of cholesterol and triglycerides under SIRT1 blocking in mice when administrated daily for 2 weeks [3]. Furthermore, APs could provide another mechanism to hinder the progression of lung cancer. By reducing VEGF expression in tumor tissues, APs (100 mg/kg) prevented the development and spread of lung cancer cells in mice significantly [93].

When given orally to mice carrying H22 cell tumors, a new cold polysaccharide (cAMPs-1A) extracted from AM significantly slowed the growth of the tumors, at dosages of 75, 150, and 300 mg/kg, with 20.53%, 36.50%, and 44.49% inhibitory rates, respectively. Furthermore, cAMPs-1A therapy may adequately preserve immunological organs, stimulate macrophage pinocytosis, and increase the proportions of peripheral blood lymphocyte subsets [94].

Astragalus membranaceus developed another novel cold-water soluble polysaccharide (APs4). MGC-803 human gastric cancer cells are significantly and dose-dependently suppressed by APs4. According to morphological results and Annexin V-FITC/PI staining, APs4-treated MGC-803 cells demonstrated standard apoptotic morphology. Cell cycle studies demonstrated that APs4 was able to stop MGC-803 cells in the S phase of the cell cycle. Additionally, APs4 therapy can affect mitochondria-dependent apoptosis in MGC-803 cells, which was primarily characterized by intracellular ROS build-up, failure of the membrane potential of mitochondria, elevation of pro- and anti-apoptotic (Bax/Bcl-2) proportions, cytochrome c release, stimulation of caspase-9/-3 expression, and poly-ADP-ribose polymerase (PARP) degradation [10].The immunosuppressive tumor microenvironment decreased the efficacy of radiation, which was thought to treat tumors by promoting the release of antigens that dendritic cells (DCs) present. APs (20 mg/kg, three times daily for 12 days) significantly slowed the development of both principal and secondary tumors that appeared following the first lesion. The TLR-4 signaling pathway is thought to be involved in the activation of DC caused by APs, as shown by phenotypic maturation and improved antigen presentation. When APs specifically encouraged DCs to go toward the tumor, where they had been activated, resulting in T-cell proliferation and a rise in the CD 4+ and CD 8+ T/ Treg proportions [95].The tumor volume and weight were decreased in BALB/c mice after transplantation of APs-induced macrophages with 4T1 tumor cells, demonstrating that the APs solution (300 g/mL for 24 h) stimulated macrophage polarisation to the M1 phenotype via the Notch signaling pathway, further enhancing anti-tumor responses and repressing tumor growth [96]. The anticancer activity of APs is summarized in Table (2).

Table (2): Anticancer activity of Aps.

Subject	Dose	Results	References
AGS cells	apatinib (20 µg/mL), and APs (200 µg/mL for 24 h)	↓ matrix metallopeptidase 9 (MMP-9) and phosphorylated AKT	[80]
non-small cell lung cancer cells	10-hydroxy camptothecin treatment and APs solution (1000 g/mL) for 24 hours	regulated mitogen-activated protein kinase 3 (MAP4K3)/and mTOR signaling pathway	[82]
SKOV3 cells	(800 µg/mL) of APs solution for 72 h	activating the JNK1/2 signaling system	[83]
prostate cancer cells	APs (0, 1, 5, 10, 20, 40 mg/ml) at various periods (0, 24, 48, 72, 96 h), respectively	↓ expression of SIRT1 in a dosage and time-dependent way	[3]
ovarian cancer cells	APs (2000 µg/mL for 24 h)	↓ inhibits PIK3CG/AKT/ Bcl-2 pathway	[84]
Human osteosarcoma MG63 cells	APs (20 mg/mL) for 24 h	↑ miR-133a expression.	[85]
hepatocellular carcinoma (H22) cells	APs (400 mg/kg/day for 15 days)	↑ IL-2 and TNF-α	[86]
RAW264.7 macrophages	APs (1000 µg/mL for 24 h)	↑ NO and TNF-α and stopping the cell cycle in the G1 phase	[87]
H22 cells	APs solution (1000 µg/mL for 72 hours)	↓ Notch1 expression	[88]
squamous cell carcinoma patient	APs (500 mL) daily following receiving the medication three times per week for 2 months	↓ pain and appetite loss	[91]
SIRT1 blocking in mice	APs (100 mg/kg) daily for 2 weeks	↓ cell proliferation of prostate cancer as well as the levels of cholesterol and triglycerides	[3]
Mice	APs (100 mg/kg)	↓ VEGF expression in tumor tissues	[93]
BALB/c mice	APs (20 mg/kg, three times daily for 12 days)	↓ primary and secondary tumors that appeared following the first lesion by regulating TLR-4 signalling pathway	[95]

4. Enhancement of the efficacy of APs

4.1. Structure alteration of APs

Several studies reported that structure modification of APs could augment the pharmacological activities of APs. This modification could be applied by multiple methods including chemical, enzymatic, or physical methods. Recent studies mainly use chemical methods for altering the structure of APs, involving selenation, sulfation, carboxymethylation, and phosphorylation [15].

Selenium (Se) is an essential trace element. Selenation of APs improved the bioavailability and efficacy. It was found that APs reacted with $SeOCl_2$ and produced Se-containing APs (Se = 16.820 mg/g) [97]. It has been conveyed that tumor growth was reduced by (23.66%) in the Se-APs group compared to the control group (51.14%), indicating that the combination APS with Se could augment the tumor inhibitory effects of APs [15]. Moreover, selenation of APs was found to improve the antioxidant effect of APs [98].

Sulfation of APs includes the reaction of sulfating reagents with polysaccharides under particular conditions, resulting in the conjugation of sulfate groups with hydroxyl groups of APs [99]. The chlorosulfonic acid–pyridine (CSA–Pyr) method is the most common sulfation method due to its high degree and yield of sulfation. The sulfated APS produced by the CSA–Pyr method had a greater anti-inflammatory and antiviral activity compared to an unmodified form of APS, in vitro and in vivo [100, 101]. Besides, sulfated APs revealed a marked antibody titer relative to non-sulfated APs. Consequently, sulfated APs could be used as [102].

Carboxymethylation is prepared by using NaOH and $C_2H_3ClO_2$ at a ratio of 16:1 at 65 °C. This type of modification upsurges the negative charge, solubility, bioavailability, and activity of APs [103]. Phosphorylation of APs also boosts their therapeutic effect and bioavailability. Phosphorated APs showed a significant antiviral effect against duck viral hepatitis and porcine virus [104, 105].

4.2. APs nanoparticles

Generally, APs were administered through injection routes. This method is associated with pain and trauma which introduces more stress to patients [106]. However, oral administration of APs is restricted because of the difficult absorption of this bulky macro-molecule through the intestine resulting in the low bioavailability of APs [13]. Usually, the low bioavailability of compounds is attributed to the low solubility and/or the low permeability that can be improved by utilizing nanoparticles or applying delivery systems for such macro-molecules [14].

At a size of 100–150 nm, nano complexes of APs and amphiphilic chitosan derivatives were prepared. Human colon adenocarcinoma (Caco-2) cells were not cytotoxic and the complex showed high penetration throughout the enterocytes [13]. Investigation of chitosan as a drug carrier for APs were conducted on LPS-injured H9c2 cell (50 µg/ml for 24 hr) and C57BL/6 mice suffered from sepsis at a dose of 200 mg/kg once a day for 3 days intraperitoneally. The complex did not induce any cytotoxicity, however, the viability increased by 20% and improved the morphology of the cardiac cells injured by LPS. Further, the nanoparticles complex diminished the bacterial loading in mice suffering from sepsis as well as exhibited anti-inflammatory properties through blocking TLR4/NF-ƘB pathway [107].

Selenium-enriched APs nanoparticles (Se-APs) also could significantly stimulate the propagation of T-lymphocytes and restrain the proliferation and migration of malignant HepG2 cells [108]. Moreover, Selenylation of APs was found to reduce its hydrodynamic particle size and reveal strong scavenger capacity against free radicals in vitro [109]. Additionally, in MCF-7 cells and in nude mice bearing MCF-7 cells, synthesis of Quercetin-3'3-dithiodipropionic acid-*Astragalus* polysaccharides-Folic acid (QDAF) effectively inhibited multidrug resistance in breast tumors [110].

Manufacture of nanoparticles containing APs and hyaluronan acid (100 nm) displayed a significant therapeutic effect against osteoarthritis (OA) by stimulating IL-1β expression as well as diminishing MMP-9, MMP-13, and TNF-α production in chondrocytes that were isolated from OA rabbit model [111].

Cocultured DCs containing PLGA nanoparticles and gold nanorods showed significant therapeutic effects against breast cancer by upregulating MHC-II, CD80, and CD86 expression. As a consequence, they significantly increased the production of TNF-, IFN-, IL-4, IL-10, and IgG1 in healthy BALB/c mice (10 mg/kg).[112]. Further, Fe_3O_4- APs core–shell nanoparticles exhibited a good therapeutic effect against iron deficiency anemia in rats by triggering hematopoietic cell generation [113]. Covering the wound of a diabetic rat with electrospun polyvinyl alcohol (PVA)/*Astragalus* polysaccharide (APs)/astragaloside IV (AS) nanofibers (145-210 nm) combined with liposomes (143.23 ± 3.25 nm) for 15 days significantly decreased the incidence of wound inflammation, improved the epithelium regeneration and collagen deposition in of diabetic rats [114].

By decreasing the expression of coagulative markers and improving antioxidant markers, APs nanoparticles at a dose of 200 mg/kg daily for 2 weeks significantly reduced cerebral thrombosis in rats [115]. Moreover, Aps nanoparticles enhanced growth, immune and anti-oxidative responses in fish that were

subjected to cold and hypoxia stress when administered for 4 weeks at a dose of 1, and 2%/kg diet [116].

APs also could serve as eco-friendly method for formulating silver nanoparticles by using 1.25 mg/mL APs and 1.0 mM $AgNO_3$ at 25 ºC. At a low concentration (0.032 to 0.063 mg/mL) and with an average diameter of 65.08 nm, this formulation demonstrated marked anti-bacterial activity against resistant bacteria including *Pseudomonas aeruginosa, Escherichia coli, Salmonella enterica and Staphylococcus aureus* [47]. To synthesize selenium nanoparticles, APs were also used as modifiers. As APS-Se NPs (10, 20 and 40 mol/L) were added to the formula, this formula showed significant antitumor activity in vitro against MCF-7 cells by increasing the apoptotic rate in a dose-dependent manner [117].

5. APs and healthy food

Foods can easily incorporate AM into their recipes, which makes it a potentially crucial ingredient. Food quality and physiological properties in general can be improved by its peculiar palatability characteristics and organoleptic properties. Since the formulated ready-to-eat food contains several bioactive compounds with numerous health benefits, it is a promising solution for treating specific health problems while increasing food consumption in people receiving treatment for health problems. In addition to being more appealing to appetite and healthier, it also contains several bioactive compounds that have numerous health benefits. As well as increasing volume, texture, decreasing water content, and extending shelf life, AM root powder can enhance the taste of food and enhance its texture. [118].

Additionally, APs inhibit glucosidase, making them useful as dietary supplements to enhance nutrient absorption [133]. The solubility and stability of flavonoids can be greatly improved by APs. Furthermore, APs have a pronounced effect on the solubilization of flavonoid aglycones, as well as on sparsely soluble compounds [119].

Regardless of dosage, herbal mixtures containing AR lengthen bread's shelf life, mitigate the staling process, and improve its microbiological stability [135]. Furthermore, dog meals may contain up to 800 mg/kg of APs without compromising palatability in a safe and effective manner. In light of this, APs may be beneficial functional additions to dog food. Pet nutritionists and researchers working in the field may find this especially interesting [136]. Antioxidant activity, immunological function, and hormone levels in the serum of lactating sows are all improved by the optimal dosage of 200 mg/kg, along with the average daily feed intake and the total lactation yield during lactation. *Astragalus* polysaccharides and soybean isoflavones can be combined to create nursing sows and create environmentally friendly feed additives [137].

Astragalus polysaccharides at a dose of 150 mg/kg can alter the composition of the cecal microbiota and serum metabolites in broilers [138]. In broiler chickens, dietary APs at a dose of 300 mg/kg resulted in a significant increase in body weight, feed intake, lymphocyte proliferation activity, the height of villi in the jejunum and the depth of the ileum's crypts (V/C), and Zonula occludens-1 (ZO-1) gene expression. It also significantly lowers intestinal pathology scores, the expression of intestinal inflammatory cytokines, the FCR, mortality rate, Helper T-cells 17/Treg (Th17/Treg), Th17, Clostridium perfringens in the cecum, Bacteroidetes, Bacteroides, Faecalibacterium, Desulfovibrio, and Butyricicoccus. Along with Romboutsia, Halomonas, propionic acid, butyric acid, formononetin, taurine, cholic acid, and equol, there is also a significant increase in Firmicutes, Prevotella, Parabacteroides, Ruminococcus, and Alistipes, and a decrease in uric acid, L-arginine, and serotonin in the ileum. Therefore, because APs regulate intestinal immune function, Th17/Treg balance, and the makeup of intestinal microbiota and metabolites, it is likely that they have an effect on intestinal inflammation in broilers exhibiting necrotic enteritis [120, 121].

Spotted sea bass grow faster and have improved physiological status when fed APs, showing its potential as a dietary supplement. The purpose of this experiment was to feed 450 spotted sea bass diets containing varying levels of APs (0, 0.2, 0.4, 0.6, 0.8, and 1.0 g/kg) for 28 days. It was found that fish weight gain, specific growth rate, feed conversion, and trypsin activity were significantly improved by dietary intake of APs. As a result, fish that fed on APs had significantly higher serum antioxidant capacity and hepatic superoxide dismutase, catalase, and lysozyme activity than fish that did not. A reduced level of triglycerides and total cholesterol was observed in fish-fed APs. The study also demonstrated that diet-induced APs downregulated the activation of hepatic acetyl CoA carboxylases 1 and 2 (ACC1), as well as peroxisome proliferator-activated receptors (PPAR), carnitine palmitamide transferase 1, and hormone-sensitive lipase (HSL). In addition, an optimal Aps dosage of 0.6881 g/kg was determined for spotted sea bass [122].

Conclusion

The immunomodulatory properties of medicinal plants and their derivatives make them extremely popular. Polysaccharide fractions could be effective immunological potentiators as well as new vaccine adjuvants, enhancing humoral and cell-mediated immunity and protecting against various viral infections. In addition to reducing blood glucose levels, APs also protect kidney function. Chemotherapeutic drugs are more effective when APs reduce tumor cell proliferation and promote cell death. Myocarditis may be treated with therapeutic agents

containing APs. APs can affect a variety of inflammatory pathways and mediators, which can interfere with the progression of inflammatory diseases. Clinical trials have not sufficiently revealed the pharmacological effects of APs. This may be caused by the AP's dosage or administration method. APs are potent enhancers and stimulants at the same time. APs research should therefore find ways to make clinical efficacy equivalent to experimental efficacy. The underlying mechanism of APs that discussed in the text are illustrated in Figure (2).

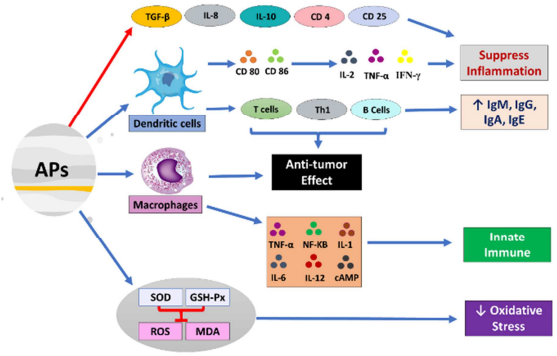

Figure 2. The underlying mechanism of APs. The blue arrows are pointing to the stimulating action and the red arrow is pointing to the blocking mechanism of APs.

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Conflict of Interest

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