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The potential of Astragalus Polysaccharide in cancer treatment

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Abstract. With the continuous development of society, people's life pressure is increasing; poor daily routines and some other factors make the incidence of cancer increasingly high. Modern medicine typically prioritizes surgical resection, radiotherapy, and chemotherapy for cancer treatment. However, these methods often result in a high recurrence rate, as well as side effects such as nausea and vomiting, which can lead to intolerant patients. Astragalus polysaccharide (APS) is extracted from Astragalus root, a water-soluble heteropolysaccharide formed by concentration and purification. Numerous studies have shown in recent years that APS can achieve anti-cancer effects in various cancers, including lung, liver, breast, and esophageal cancers. It can suppress tumor cell growth, cause tumor cell death, and obstruct tumor cell invasion and metastasis by modulating the body's immune system. Additionally, when combined with other chemotherapy drugs, there is evidence that APS can improve efficacy and reduce toxicity. In this paper, we review recent research on APS in the field of anticancer therapy, aiming to provide a valuable reference for future studies.

Keywords: Cancer treatment, Astragalus, Astragalus polysaccharide.

1. Introduction

Cancer is caused by abnormal growth of cells, which can occur in any organ or structure, and consists of tiny cells that have lost their ability to stop growing. It is currently the leading cause of human death in the world, and it has also severely hindered the growth of human life expectancy [1]. Lung cancer currently constitutes the primary cause of mortality. For cancer, modern medical methods of treatment mainly include surgical operations, radiotherapy, chemotherapy, and newly developed immunotherapy. While treatment has extended the survival time for cancer patients, most patients still face the possibility of recurrence and cannot survive for an extended period [2]. Traditional Chinese medicine has multiple therapeutic targets, minimal side effects, and demonstrated efficacy in cancer treatment. It can extend patient survival and improve their quality of life [3]. For example, Ganoderma lucidum, commonly used in Chinese medicine as a home health care product, has been found to inhibit the invasion of MDA-MB-231 cancer cells in breast cancer cells by down-regulating the expression of related receptors in spores and unpurified fruit [4,5].

Astragalus polysaccharide (APS) is a kind of polysaccharide extracted from Astragalus root and is one of its key active components of Astragalus. It has various functions, including regulating immunity, providing antioxidant effects, delaying aging, and exhibiting anticancer properties [6]. The results of related vivo and in vitro experiments showed that APS had an obvious anti-tumor effect. Nowadays, the

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anti-tumor mechanism of APS has garnered significant attention from various experts and scholars. However, the current understanding of this mechanism reveals that it is not a single mechanism but a complex regulatory process involving multiple mechanisms. Relevant studies have shown that APS can suppress cancer by boosting the immune response [7], promoting apoptosis in cancer cells, triggering their autophagy mechanism, and influencing the tumor microenvironment. When APS is combined with other methods of cancer treatment, it can markedly enhance therapeutic efficacy and diminish hazardous side effects [8]. APS can inhibit many kinds of solid tumors. In this article, we will clarify the potential of APS for cancer treatment, the mechanism of action, and the current research status.

2. Biological Properties Action of APS

APS is a mixture of glucose, mannose, fructose, galactose, glucuronic acid, and galacturonic acid [9]. These monomers are connected by a type glucoside bond. Researchers discovered that APS could boost the immune response in mice, enhance the function of macrophages, stimulate the proliferation of DC precursor cells, and improve the proliferation and antigen presentation ability of T cells [10, 11]. APS can elevate glutathione levels, superoxide dismutase (SOD), overall antioxidant capacity, and anti-hydroxyl radical activity. It can also stop MDA from forming. APS can also protect mitochondria from oxidative damage by stopping the change in mitochondrial permeability and making antioxidant enzymes work better [12]. Additionally, APS exhibits anti-inflammatory properties by reducing inflammatory damage. It can suppress inflammation by obstructing the activation of NF-κB p65, consequently impeding signaling pathways and diminishing the expression of intercellular adhesion molecule-1 (ICAM-1) and IL-8 [13]. It can also indirectly inhibit inflammation by scavenging oxygen-free radicals and further inhibit NF-κB p65 to prevent its activation [14]. The anti-cancer mechanisms of APS include influencing immune cells, promoting apoptosis of cancer cells, triggering autophagy of cancer cells, and thus regulating the microenvironment of tumors. When combined with other treatments, APS can improve treatment effectiveness while reducing toxic side effects [15]. Studies have shown that it is not only non-cytotoxic but also can reduce the toxicity of drugs used in cancer chemotherapy and assist in the treatment of cancer. It provides protective effects on the bone marrow hematopoietic microenvironment, thereby reducing adverse reactions [16].

3. Anti-cancer mechanism of APS

APS can substantially impede the proliferation of cancer cells by disrupting the S, G2/M, and G0/G1 phases of the cell cycle [17]. Some studies have shown that APS-SENPS nanoparticles can greatly raise the total number of HepG2 cells that get stuck in the S phase, which then kills the cells by damaging the mitochondria [18]. Moreover, APS can impede the proliferation of cancer cells by modulating multiple signaling pathways, including PI3K/Akt, ERK/MAPK, and NF-κB [19]. For example, APS inhibited NF-κB activation, reduced Bcl-xL protein levels, suppressed the proliferation of NCI-H358 and A549 cells, and slowed the growth of A549 xenografts in animal models [20]. During APS-induced apoptosis, the main genes and proteins involved include wild-type p53, caspase, Bcl-2 family, etc. Relevant research shows that APS can promote apoptosis of lung cancer cells through regulating the expression of Notch1/3 level and caspase-8 in tumor tissue [21]. Experiments indicate that APS may downregulate miRNA-27a expression, consequently up-regulating FBXW7 expression, which ultimately inhibits proliferation and induces death in ovarian cancer cells. Moreover, numerous studies have demonstrated that APS can enhance the immune microenvironments of tumors by modulating immune cells, including macrophages (M), dendritic cells (dc), myeloid-derived suppressor cells (MDSCs), T cells, regulatory T cells (Tregs), natural killer cells (NK), and B cells, thereby augmenting the immune response in tumor patients. Enhanced immune cell efficacy in eliminating tumor cells can significantly impede tumor growth and spread.

APS can induce the production of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), and various other cytokines through the Notch signaling pathway, hence enhancing the polarization of M1/M2 macrophages. It stimulates M1 macrophages and suppresses M2 macrophages, consequently augmenting the cytotoxic and phagocytic capabilities against tumor cells

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and restraining their proliferation and spread [22]. Additionally, APS improves immunosuppression by activating the tumor-killing function of M1 macrophages and T cells within the tumor microenvironment [23]. Dendritic cells (DCs) serve as specialized cells that present antigens. Immature DCs require specific signals to mature [24]. Once mature, dendritic cells effectively enable naive T lymphocytes to be activated and play a key role in the immune response. Experimental results show that APS promotes DC maturation, enhances their antigen-presenting ability, improves the precision of tumor cell targeting, and inhibits tumor growth [25]. In Chang W et al.'s experiment, DCs treated with APS significantly increased the proliferation of CD4+/8+ T cells in breast cancer mice. Further experiments confirmed that a DC-based anti-tumor vaccine increased expression of CD86, CD80, and CD40 on the surface of DCs and served to inhibit the growth and metastasis of breast cancer cells [26]. MDSCs constitute a set of pathologically activated myeloid cells with phenotypic and immunosuppressive characteristics [27]. It was found that APS can decrease the quantity of MDSCs and restrain the expression of Arg-1, TGF-β, and IL-10. It diminishes the immunosuppressive function of MDSCs in melanoma mice and enhances the cytotoxic capacity of CD + 8T cells against tumor cells, consequently decreasing tumor proliferation in tumor-bearing mice [28]. Tregs are a subtype of T lymphocytes that modulate the immune response, partially inhibiting the body's normal immunological activity and facilitating tumor cells' evasion of immune monitoring. Li Q et al. found that APS can inhibit the activity and function of Treg cells. APS can also inhibit Tregs recruitment through the CXCR4/CXCL12 signaling pathway mediated by stromal cell-derived factor-1 (SDF-1), thereby inhibiting Tregs cell migration. Keep the tumor cell-killing effect of normal immune cells [29]. APS can suppress TGF-β expression by activating the TLR4 signaling pathway, hence diminishing the population of immunomodulatory Treg cells [30].

4. APS in Cancer Treatment

In order to explore whether APS exerts anti-colon cancer and immunomodulatory effects through the signaling pathway of TLR4/MyD88/NF-κB, Zhang et al. administered APS to both TLR4+/+ and TLR4-/-Lewis lung cancer mice. The aim of this study was to investigate the impact of APS on TLR4/MyD88/NF-κB signaling pathway related protein expression and Th1/Th2 cytokine level in two types of mouse tumor tissues. The results showed that in TLR4+/+ mice, APS decreased the expression of TLR4, MyD88, NF-κB p65 proteins, and mRNA in tumor tissue, increased TH1 cytokine levels in spleen tissue, and decreased TH2 cytokine levels in a dose-dependent fashion. These effects, however, weren't seen in TLR4-/- mice. Moreover, in comparison between the model group and different concentrations of APS groups, the expression of TLR4, MyD88, NF-κB p65 proteins and mRNA in tumor tissue and Th1/Th2 cytokine in spleen tissue of mice had no statistical significance. The findings indicate that APS may exert anti-tumor and immunomodulatory actions through the TLR4/MyD88/NF-κB pathway [31]. Zhou and others studied the effects of APS on macrophages and EAC mice. They found that APS increased the tumor necrosis factor α, nitric oxide, and IL-6 levels, but this action was reduced in the existence of TLR4 inhibitors or MyD88 inhibitors. After 25 days of oral administration of APS, it resulted in an increased apoptotic rate of tumor cells and better immune organ indices in a mouse model. It also reduced the tumor weight, but the effect was not significant in tumor-bearing mice with TLR4 or MyD88 gene defects. These findings indicate that APS may modulate host immunity by activating the MyD88-dependent signaling pathway, hence enhancing its anticancer effects [32]. To investigate the effect of APS on hepatocellular carcinoma, Lai and his colleagues administered various doses of APS to mice with H22 tumors. The outcome showed that APS could inhibit the growth of H22, and in the 400 mg/kg dose group, the tumor suppression rate achieved 59.01%. APS markedly enhanced the metrics of the spleen and thymus and increased serum TNF-α and IL-2,6 concentrations. These results indicate that APS has antitumor activity and affects immune regulation [33].

APS combined with cytotoxic chemotherapy and targeted small-molecule drugs can play a synergistic role in anticancer therapy by reducing drug toxicity and delaying or inhibiting tumor drug resistance. In H1299 lung cancer cells, APS combined with 10-hydroxycamptocampine can inhibit the MAP4K3/mTOR signaling pathway, followed by the inhibition of cell migration and invasion [34]. Yang et al. exhibited a substantial synergistic effect on the growth inhibition of nasal cancer cell lines

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when APS was administered in conjunction with cisplatin. Compared to cisplatin alone, the combination promoted apoptosis in CNE-1 cells; the cell counts of G0/G1 and S phase were increased, while the cell count of G2/M phase was decreased [35]. Wu et al. discovered that in the treatment of pancreatic cancer, the combination of APS and Apatinib further down-regulated the expression of p-AKT, p-ERK, and MMP-9, remarkably enhancing the inhibition of pancreatic cells' migration, proliferation, and invasion [36]. In clinical trials involving patients with related tumors, APS was found to alleviate a range of symptoms caused by tumors, such as pain, nausea, and vomiting. Additionally, it reduced the impact of chemotherapy drugs on patients' immune function and minimized chemotherapy side effects, thereby improving patients' quality of life [37].

5. Summary

APS is the main active component of Astragalus, which has significant anti-tumor and immune function enhancement effects. Numerous in vivo and in vitro experimental results show that APS is able to restrain the multiplication of cancer cells and boost the apoptosis of cancer cells through regulating related pathways, regulating immune responses, improving tumor microenvironment, etc. Some experiments have also confirmed that APS can not only enhance the therapeutic effect when combined with some certain chemotherapy drugs (such as cisplatin, paclitaxel, etc.), but also reduce the adverse reactions following chemotherapy and enhance the immune response and quality of patients' lives, which can be described as the best of both worlds. Although APS has been proved to have a good prospect in the application of anti-tumor, it still faces many problems at this stage. For example, at present, most of the anti-tumor studies of APS are limited to in vitro or in mice, and the evidence of relevant clinical trials is insufficient, so more reasonable and reliable clinical studies are needed to provide evidence support. In addition, under normal circumstances, when APS is used in combination, the anti-cancer effect increases as the concentration and time increase, but the specific dose and time for clinical patients remain to be clarified. Therefore, as research into the antitumor mechanisms of APS continues to advance, it will provide a more detailed and precise theoretical foundation for its application in cancer treatment, potentially expanding its clinical use.

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