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# *Research on the Mechanism of Huangqi Polysaccharides in Cervical Cancer*

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***Abstract.*** Cervical cancer is an important malignancy threatening the health of women that has been extensively studied lately due to its impressive anti-tumor and immunomodulatory experiences. Astragalus Polysaccharide (APS), also the primary active constituent of the traditional Chinese medicine Astragalus, is generally gaining immense attention because of its impressive anti-tumor and immunomodulatory properties. As part of the immune system APS both regulates the immune response and directly kills tumor cells: it triggers tumor cell apoptosis and remodels the immune microenvironment to augment the immune response, thereby complementing each other in fighting the tumor. Also, it can affect ERS signaling pathway and enable the reversal of epithelial-mesenchymal transition (EMT) process, inhibition of tumor invasion and metastasis, as well as the increase of the sensitivity of chemotherapy drugs. This paper examines the mechanism of synergy of APS in directly killing tumor cells, multifaceted immune control, and chemosensitization, which have the great potential to help in an adjunct therapy of cervical cancer, provides a theoretical background of development of the new treatment methods, as well states the single shortcoming of clinical application due to the absence of standardized portocol.

***Keywords:*** Cervical cancer, stragalus polysaccharides, apoptosis, immune regulation, synergistic mechanism

## 1. Introduction

Cervical cancer is one of the greatest global health challenges of women. It currently ranks as the fourth most commonly diagnosed cancer in women globally [1]. While developed nations have witnessed a marked decline in cervical cancer incidence in recent years, thanks to socioeconomic and healthcare advancements, the incidence and mortality rates of cervical cancer in developing countries remain high. The incidence and mortality rates of cervical cancer in China have generally been on the rise, and there are significant regional and demographic differences. The main areas showing higher mortality rate are in central and western part and the age of onset shows young trend [2]. The existing therapies are surgery, radiotherapy as well as chemotherapy. Even though these methods are capable of significantly managing the condition and extending the lifespan, they frequently present themselves with unwanted side effects that may include issues with the digestive tract, immunosuppression and renal toxicity that severely affect the quality of life of the patients [3]. The traditional Chinese medicine has proved to have distinctive benefits and opportunities when it

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comes to the diseases. It has the ability to control the diseases, decrease the side effects of radiotherapy and chemotherapy, when it comes to the pains of the cancer. During the recent years, it has become a research hot spot [4].

As a key active constituent of the traditional Chinese medicine Astragalus, Astra galus Polysaccharide (APS) is a compound that has been receiving so much attention over the last few years because of his remarkable immunomodulatory and anti-tumor and potency. Research has also revealed that the mechanism through which astragalus polysaccharides have anti-malignant tumor effects might primarily involve the regulation of tumor immunity, the inhibition of tumor cell proliferation, tumor cell invasion and tumor cell metastasis, the induction of apoptotic cell death and the increased effect as well as decreased toxicity of chemotherapy drugs, in the event of administering combination therapy [5]. The existing studies carried on APS are primarily directed at the killing or prevention of tumor cells, and the improvement of the immune action of the body in this or that aspect [6]. The objective of the study is to refresh the research progressiveness in the mechanism of action of astragalus polysaccharides in cervical cancer, as well as to thoroughly familiarize its anti-tumor action and multi-target immune regulation to offer theoretical rationale in creating new treatment plans to cervical cancer as an adjuvant agent.

## 2. The pathogenesis of cervical cancer

Human papillomavirus (HPV) infection is the primary driving factor for the occurrence of cervical cancer. The core mechanism of the pathogenesis lies in the interaction between the E6 and E7 oncoproteins of high-risk HPV (HR-HPV) and the host tumor suppressor proteins p53 and Rb,The inactivation of these two key pathways is the primary step in the transformation of cells into malignancy. HPV infection begins in the proliferative basal or basal lateral cells,its DNA initially existed in a free state and replicated itself, however, free HPV DNA can induce chromosomal instability and aneuploidy to promote viral integration. Upon integration of HPV DNA into the host genome, especially when the integration process disrupts the E2 gene region of the virus itself,the expression of E6 and E7 will lose transcriptional control, thereby acquiring the potential to transform cells. Integration is a crucial step in the transformation of cervical intraepithelial neoplasia (CIN) to microinvasive cancer [7], It will interfere with the regulation of the cell cycle and the mitotic apparatus, leading to abnormal chromosome numbers and structures, and causing abnormal regulation of cell cycle proteins such as cyclin D and cyclin E [8] .In addition, the E6 protein binds to p53 through the ubiquitination pathway, inactivating and degrading it, thereby inhibiting cell apoptosis and increasing chromosomal instability, promoting excessive cell proliferation. The E7 protein, on the other hand, preferentially binds to the non-phosphorylated pRb, causing the dissociation of the pRb-E2F complex. The free E2F then acts as a transcription factor, leading to the overexpression of p16INK4A, resulting in uncontrolled cell cycle transcription and excessive cell proliferation. Research shows that the expression level of p16INK4A is closely related to the severity of the disease and HR-HPV infection, and can establish it as a valuable diagnostic biomarker for cervical cancer. Thus, the essential pathological basis of the occurrence of cervical cancer is two functional violations of not only the p53 pathway (p54-MDM2-p53) but also the Rb pathway (p16-CDK4/cyclin D1-pRb) is the violation of the G1 pathway as a whole [9].

Telomerase activation is also an important factor of the pathological process. The telomerase activity is inactive or insignificant in normal epithelial CIN1 and increases significantly in CIN3 and squamous cell carcinoma (SCC), where HR-HPV activates telomerase activity via E6 (The activity does not require the degradation of p53), and the telomerase mechanism plays an active role in promoting the malignant progression and cell immortalization in collaboration with the degradation

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of p53. TGF-G tumor growth factor, both in the initial phase, which consists of precancerous lesions, HPV E6 and E7 may down-regulate the expression of TGF-E6, and, therefore, relieve its suppression of E6/E7 and its blocking of p53 and pRb; and in the metastatic stage, the cervical cancer cells become resistant to the inhibition power of TGF- beta, which leads to the increased level of TGF. This has a direct effect of stimulating the growth of tumor cells, as well as, increasing the local immunosuppressive effect, which contributes to the tumor avoiding immune surveillance [10].

Moreover, the incapacity of the host immune system is also one of the central prerequisites in the continuous progress of cervical cancer.HPV achieves immune evasion through various means, such as avoiding the presentation of immunogenic capsid proteins in the early stage of infection, not inducing the production of interferon (IFN), E6 and E7 inactivating the intermediate products of the IFN cascade reaction, and restricting the release of viral particles without damaging the cells, thereby avoiding triggering inflammation and immune responses. Because the transformed squamous cells are located on the outer layer of the mucosa, while immune surveillance is mainly in the submucosal layer, the virus can effectively evade local immunity. The ineffective responses of T cells to HPV E2 and E6 further exacerbate immune suppression and increase the risk of cervical cancer [11]. These complex mechanisms jointly initiate the pathogenesis and progression of cervical cancer, providing a rationale for exploring the anti-tumor effects of APS.

## 3. The mechanism of ginseng polysaccharides in preventing cervical cancer

### 3.1. The main active components of Astragalus

Astragalus, as a representative of tonic Chinese medicines, has the functions of strengthening the “qi”, raising the “yang”, consolidating the exterior and stopping sweating, promoting the excretion of toxins and promoting tissue regeneration, as well as promoting urination and reducing swelling. In recent years, accumulated clinical and pharmacological investigations have revealed that astragalus has anti-tumor effects both in vivo and in vitro [12]. Its active ingredients mainly include astragalus polysaccharides, astragalus saponins, astragalus total flavonoids, etc. Among them, APS stands out for its notable immunomodulatory and anti-tumor activities, which have drawn significant research interest.

### 3.2. APS directly induces apoptosis of tumor cells

APS induces apoptosis in cervical cancer cells through mitochondrial and death receptor pathways, halts the cell cycle progression, and directly inhibits the proliferation of tumor cells. Studies have shown that APS can upregulate the expression of pro-apoptotic proteins (such as Bax and Caspase-3), downregulate anti-apoptotic proteins (such as Bcl-2), and activate the endogenous apoptotic pathway; at the same time,it induces exogenous apoptosis by activating the Fas/FasL signaling [5]. Furthermore, APS can arrest cells in the G0/G1 phase by suppressing the expression of cyclin D1 and CDK4/6,and interfere with the cell cycle process, thereby inhibiting the proliferation of tumor cells [13].

### 3.3. The influence of APS on immune cells

Macrophages originate from precursor cells, presented in almost all tissues of the body, in the bone marrow and play a very important role in immune reactions. They can directly engulf and kill foreign pathogens, also activate the body's lymphocytes or other immune cells to indirectly mount

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an immune response against the pathogens, thereby protecting the body's tissues and organs from being invaded by foreign pathogens [14]. Some scholars have classified macrophages into M1 type and M2 type. These two types play different roles in the tumor microenvironment-M1 macrophages inhibit tumor growth, while M2 macrophages inhibit tumor growth. M1 macrophages can produce nitric oxide (NO), reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and a large number of pro-inflammatory cytokines, such as interleukin-1, interferon gamma (IFN-γ), and tumor necrosis factor α (TNF-α), and they specifically present antigens, participate in the positive immune response of the body, and exert killing and phagocytic effects on tumor cells, playing a crucial role in inhibiting the growth and metastasis of tumor cells. On the contrary, M2 macrophages secrete high levels of anti-inflammatory cytokines — including IL-4, IL-10, and IL-13, which to some extent inhibit normal immune response and promote tumor cell growth and invasion. Thus, strategies that activate M1 macrophages, suppress M2 polarization, and adjusting the ratio of M1/M2 macrophages [14].

NK cells have a broad-spectrum anti-tumor effect and can directly kill tumor cells without the need for pre-treatment with antigens. Its killing mechanism mainly includes inducing apoptosis of target cells, releasing effector cytokines, and mediating antibody-dependent cell cytotoxicity (ADCC), etc. When the functions of T cells and B cells in the body are impaired, NK cells play an especially crucial role in immunity.By inoculating the human squamous cell carcinoma cell line GNM under the skin of nude mice, Liu established a tumor transplantation model to explore and observe the inhibitory effects of astragalus, penicillamine, and their combination therapy on the transplanted tumors [15]. The results showed that the density of spleen cells and the activity of NK cells in the ginseng monotherapy group and the combined therapy group were significantly higher than those in the penicillamine group and the control group ($P < 0.01$), indicating that ginseng can effectively improve the activity of NK cells and participate in the immune response of the body. In addition, APS can synergistically promote the proliferation and activation of NK cells with IL-2, effecting significantly better than that of using IL-2 alone, and it shows a non-simple additive synergistic effect.

### 3.4. APS regulates the immune function of the body through multiple dimensions

The mechanism of APS's immunomodulatory effect is a complex process involving multiple targets and multiple levels. It mainly enhances the overall immune function of the body by activating both innate immunity and adaptive immune responses in a synergistic manner. Multiple studies have revealed that astragalus and its active components have a definite enhancing effect on the function of T lymphocytes. Zhangfound that both the concentrated extract of Astragalus membranaceus and the serum of mice containing Astragalus could promote the proliferation of spleen lymphocytes in mice, enhance the mixed lymphocyte culture response, and increase the production of IL-2. Moreover, these effects were all dose-dependent, indicating that Astragalus can effectively activate T-cell immune responses both in vivo and in vitro [16].

The extract of astragalus can increase the secretion level of IL-2 in cells and has an inhibitory effect on IFN-γ. Moreover, this effect shows a dose-dependent pattern. In tumor-bearing mice, APS can also significantly promote the proliferation of T and B lymphocytes, enhance the secretion of cytokines such as IL-2 by spleen cells, and induce the production of tumor necrosis factor in peripheral blood mononuclear cells of healthy individuals and tumor patients in vivo. Furthermore, APS can further promote the synthesis of IL-2 by lymphocytes and the expression of its receptors, and stimulate macrophages to produce IL-1. This latter substance then enhances the biological

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activity of TNF. These multi-target regulatory mechanisms jointly reshape the tumor immune microenvironment.

### 3.5. The impact of APS on enhancing the sensitivity of chemotherapy drugs

The mechanism by which astragalus polysaccharides (APS) improve the sensitivity of cancer cells to the chemotherapy drug cisplatin (DDP) for cervical cancer mainly involves regulating the endoplasmic reticulum stress (ERS) and autophagy-related pathways, reversing the chemotherapy resistance of tumor cells, and promoting their apoptosis. Through in vivo experiments, it was found that when cisplatin was used alone, the expressions of endoplasmic reticulum stress marker proteins GRP78 and CHOP, as well as autophagy marker proteins LC3-II and apoptotic execution protein Caspase-3, all increased in the transplanted tumors of cervical cancer HeLa cells [17]. This suggests that while cisplatin kills tumor cells, it may also induce protective ERS and autophagy, thereby weakening its efficacy and leading to drug resistance. However, when APS was combined with DDP, the expression of these proteins showed a dose-dependent further significant increase ($P < 0.01$). Such an outcome suggests that APS does not just suppress or promote ERS and autophagy, but can possibly create its effect by controlling the balance between the two. In particular, APS can additionally increase the levels of ERS to the irreversible point triggering ERS to transition into an apoptosis-stimulating signal. It does so by strongly increasing the expression of pro- apoptotic proteins e.g. CHOP, further overwhelming the protective effect of large GRP78 expression, and orienting the stress response that occurs in response to DDP to full cell apoptosis. Moreover, in the case of autophagy the APS can be an important contributor to the elevation of the LC3-II level hence over-activation of the protective autophagy brought about by DDP in a form that is cytotoxic, and thus suppressing cellular homeostasis and facilitating cell death rather than serving as a protective domain against which the cells can survive. These pathways eventually lead to the activation of Caspase-3 which collectively carries out the cell program of apoptosis.

Overall, the most fundamental theory, the mechanism through which APS increases the sensitivity of chemotherapy, is the possibility to control the pattern of stress responses of tumor cells under the influence of chemotherapy drugs. That is, by pushing the protective ERS and autophagy induced by DDP to an irreversible damage level, it promotes tumor cell apoptosis, reduces their drug resistance, and achieves the effect of chemosensitization.

## 4. The clinical application potential and limitations of APS

Astragalus, as a traditional Chinese medicine, its active component astragalus polysaccharide (APS) has a broad clinical application foundation in areas such as diabetes, antibacterial, antiviral and anti-tumor [18]. Clinical studies have shown that APS can alleviate the toxic side effects associated with radiotherapy and chemotherapy, enhances patient quality of life, and demonstrate a promising potential as an adjuvant treatment [18]. Xia explored the differences between the two groups through a randomized controlled trial design of patients treated with radiotherapy and chemotherapy. The groups of patients receiving combined therapy with astragalus polysaccharides were compared in regard to immune activity, alleviation of traditional Chinese medicine symptoms, management of side effects, and tumor markers [19]. By utilizing the results, one can conclude that APS as an adjunctive way of treatment can help to dramatically boost the immune capabilities of patients. It is reflected in the rise of the proportion of CD3+ and CD4+ cells and the CD4+/CD8+ ratio and a decrease in the number of CD8+ cells and myeloid-derived suppressor cells (MDSC), which means that it eliminates T cell subsets and improves the anti-tumor immune response of the body.

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Although APS has shown positive effects in anti-tumor adjuvant therapy, there are still several issues that need to be addressed urgently. In particular, there is no standardized protocol for its clinical application, such as whether it can be used as the primary treatment drug, or if it can be combined with other drugs and the appropriate dosage. Moreover, most of the current studies are small-sample or single-center trials, lacking high-level evidence-based medical evidence. Moreover, the traditional administration method of APS, such as oral administration, has a relatively low bioavailability, which limits the full exertion of its therapeutic effect.

## 5. Conclusion

APS demonstrates multi-target therapeutic potential in the treatment of cervical cancer through three mechanisms: directly inducing apoptosis of tumor cells, multi-dimensional activation of the body's immune system, and enhancing the sensitivity of chemotherapy drugs. It is not only able to enhance the activity of NK cells, regulate the function of macrophages and balance the T lymphocyte subgroups, but also used for synergistically enhance the anti-tumor immune response through the cytokine network, while alleviating the toxic side effects of radiotherapy and chemotherapy and improving the quality of life of patients. However, the existing researches still exist limitations such as limited sample size, lack of long-term follow-up, and absence of high-level evidence-based medical evidence. In the further, exploring the synergistic mechanism between APS and existing therapies are potential directions. New drug delivery systems like nanocapsules can be explored to enhance targeting ability and bioavailability, providing new directions for the development of integrated traditional Chinese and Western medicine treatment strategies for cervical cancer.

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