Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/57/20241314

Mechanism of Astragalus polysaccharides (APS) improving myelosuppression and exerting anti-tumor effects during radiotherapy and chemotherapy

Jiani Li

First Clinical Medical College, Guizhou University of Traditional Chinese Medicine, Guiyang, Guizhou, 550000, China

lijiani@gzy.edu.cn

Abstract. Chemoradiotherapy, as a routine method of anti-tumor treatment, is accompanied by severe adverse reactions such as myelosuppression. It not only hinders the treatment process but also reduces the quality of life of patients. Therefore, effective prevention and treatment of myelosuppression during radiotherapy and chemotherapy is an extremely important issue that needs to be addressed in clinical practice. The commonly used method for preventing and treating myelosuppression during radiotherapy and chemotherapy is medication intervention. Human granulocyte colony stimulating factor(Human G-CSF) is the preferred drug, while modern Chinese medicine preparations are used as adjunctive therapy. There are still certain limitations in the clinical use of Human G-CSF, so research on the unique role of modern Chinese medicine in this regard has gradually received attention. By consulting literature, we took Astragalus polysaccharide (APS), a traditional Chinese medicine extract that has been proven to have relevant preventive and curative effects in existing studies, as an entry point to explore the mechanisms involved in the modulation of the signaling pathway by APS to play a role in improving the myelosuppressive and anti-tumour effects. This study aims to explore the mechanism by which APS participates in regulating signaling pathways to improve myelosuppression and anti-tumor effects. Some of its mechanisms are closely related to traditional Chinese medicine theory. This article will briefly discuss them in order to provide some inspiration for expanding drug selection in clinical practice and further conducting related research.

Keywords: APS, myelosuppression with radiotherapy and chemotherapy, traditional Chinese medicine, pharmacological effects and mechanisms

1. Introduction

Chemoradiotherapy induced myelosuppression refers to one of the most frequent adverse reactions during anti-tumor treatment. Chemoradiotherapy inhibits bone marrow hematopoietic activity, decreases the number of blood cells, reduces their resistance and self repair ability, and in severe cases, may cause infections, anemia, and so on. It becoming the main obstacle to promoting treatment and improving prognosis. The commonly used drug for treating myelosuppression in clinical practice is polyethylene glycol recombinant human granulocyte colony stimulating factor (PEG-rhG-CSF). Its main action is to promote the growth of peripheral blood cells, but it has more adverse reactions, most

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commonly occurring in the skeletal and digestive systems. Moreover, this drug is expensive and only effective for a short period of time, which makes it difficult to disseminate [1,2]. Existing studies have shown that modern Chinese medicine has the advantages of multi-targets, multi-links, wide sources and high safety [1,3]. It has been widely used in the treatment of myelosuppression after radiotherapy and chemotherapy. From the perspective of traditional Chinese medicine theory, radiotherapy and chemotherapy are classified under the category of heat toxin [4]. Heat is injurious to fluids, and fluids and blood are homologous to each other, thus chemoradiotherapy can cause depletion of fluids and blood in the body. The concept of myelosuppression caused by radiotherapy and chemotherapy in Western medicine is highly consistent with the traditional Chinese medicine belief that heat toxin tend to deplete the body's fluid and blood. In terms of treatment principles and methods in traditional Chinese medicine, as the saying goes, 'deficiency is replenished', 'loss is gained', and 'supplementing Qi and generating blood'. Therefore, in clinical practice, drugs with sweet taste, warm nature, and the effect of generating fluids and nourishing blood are often used for tonifying [5] to improve the body's immune system and promote hematopoietic function. Research has shown that Astragalus membranaceus has the highest frequency of occurrence in the prevention and treatment of myelosuppression after radiotherapy and chemotherapy among Chinese medicinal herbs for tonifying deficiency [3,4].

APS is an effective active ingredient extracted from Astragalus membranaceus that has a Qi tonifying effect. Modern research suggests that it has pharmacological effects such as promoting hematopoiesis, enhancing immune function, and protecting bone marrow [6,7]. This article will start from the theory of traditional Chinese medicine and briefly introduce the effect of APS on p53-p21 to improve myelosuppression during radiotherapy and chemotherapy, as well as Wnt/β-catenin exerts anti-tumor effects through two signaling pathways is expected to provide new insights for the further application of modern traditional Chinese medicine in the clinical treatment of myelosuppression after tumor radiotherapy and chemotherapy.

2. Mechanism of action of APS

2.1. Analysis of active ingredients

APS was isolated and extracted from Astragalus membranaceus from a class of biomacromolecular compounds consisting of glucan (Glu) (including water-soluble glucan and water-insoluble glucan), heteropolysaccharides (mostly acidic heteropolysaccharides, including glucose, arabinose, rhamnose, galactose, and glycoalkaloid acid, etc.), and some proteins that may be contained as well as trace elements, as polysaccharides contain many branched chains and a large number of hydroxyl groups. Their chemical structures are extremely complex and difficult to determine [8,9]. Some studies have shown that APS is mainly composed of glucose, galactose, arabinose and other monosaccharides linked by β-1,4-glycosidic bonds to form a linear polysaccharide structure [10]. Different Astragalus species, origins, and preparation methods may lead to differences in the chemical composition of APS, which may affect its biological activity. APS mainly has immunomodulatory, anti-tumour, hematopoietic and bone marrow protection pharmacological effects.

2.2. p53-p21

p53 is an important transcription factor involved in the regulation of apoptosis. Tang Shihuan et al. [11] found that p53-p21 is involved in the process of stem cell senescence, and once this pathway is activated, the self-renewal ability of stem cells is reduced, thus inducing cell senescence or even apoptosis. APS may be able to reduce the damage to hematopoietic stem cells (HSCs), enhance their self-repairing ability, and allow more cells to participate in the cell cycle by reducing the expression of p53 and inhibiting the aberrant activation of p53-p21 signaling pathway associated with stem cell senescence, in order to slow down the senescence of HSCs. see Figure 1. Modern Chinese medicine attributes chemoradiotherapy to the category of heat toxin, and a high level of heat can easily deplete the body's fluid and blood, resulting in a relative deficiency of Qi and blood. Astragalus is a sacred medicine for tonifying Qi, which has the efficacy of generating fluids and nourishing blood. Chinese medicine is

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based on the theoretical foundation of 'Qi and blood mutualisation' and 'Qi can generate blood', and has always had the principle of 'tonifying Qi and generating blood', which is considered to be the most effective way of treating the problem of blood circulation. It is believed that by using a large number of Qi tonic products, the tangible yin and blood can be generated. APS can reduce the expression of pro-apoptotic gene/protein p53 and inhibit the activation of this pathway by acting on the p53-p21 signaling pathway, thus enhancing the self-repairing ability of HSCs, slowing down the aging of HSCs, and inhibiting apoptosis, which is consistent with the traditional Chinese medicine theory of 'when positive qi exists in the internal body, evil can not be interfered with'. This statement is from the classic Chinese medical text 'The Inner Canon of Huangdi', which means that if the body has sufficient positive Qi, it will not be easily attacked by external evils to cause disease. Many studies have suggested that positive Qi may be related to the immune system. Modern pharmacological studies have shown that APS does have the effects of regulating the immune system, delaying the aging of HSCs, inhibiting apoptosis of HSCs, and treating chemotherapeutic myelosuppression [1,7].

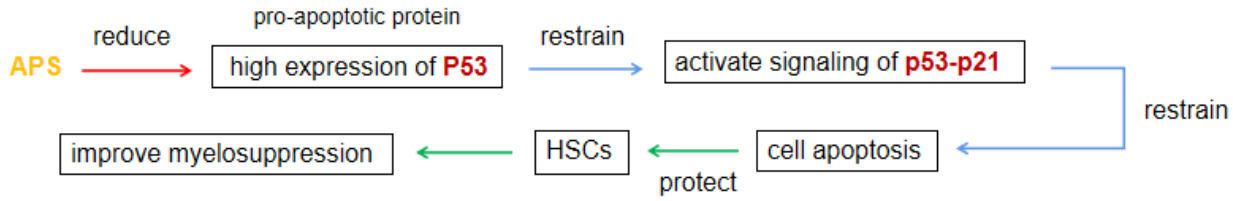

Figure 1. Mechanism of improved myelosuppression by APS.

2.3. Wnt/β-catenin

The classical Wnt/β-catenin signaling pathway (β-catenin-dependent) is mainly involved in the regulation of the cell cycle and a variety of biological functions, and is particularly closely related to cancer development [12]. It has been shown that lowering the expression of Wnt1 ligand can inhibit the aberrant activation of the Wnt/β-catenin signaling pathway, thereby slowing down the proliferation of cancer cells in mouse models of breast cancer. On the contrary, if Wnt1 is overexpressed, it promotes tumour growth [13]. A study by Tan Wenchao et al. [14] also found that APS significantly down-regulated the expression of Wnt1 and β-catenin proteins in a dose/concentration-dependent manner, which in turn inhibited the proliferation of breast cancer cells, and to a certain extent reduced the probability of tumours developing distant metastasis and/or invasion. Experiments showed that the 4.0 mg/mL APS administration group was able to further reduce the expression of Wnt1 and β-catenin protein compared with the 2.0 mg/mL APS administration group. See Figure 2, the mechanism by which APS acts on the classical Wnt/β-catenin signaling pathway to exert anti-tumour proliferation and differentiation effects (Figure 3).

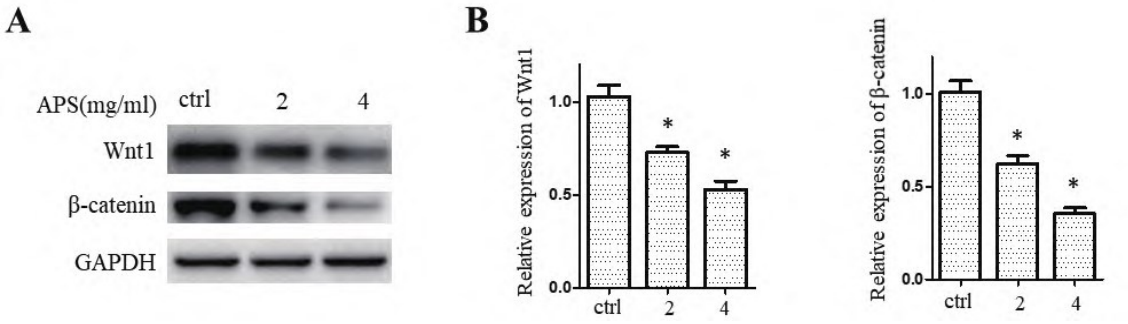

Figure 2. Expression of Wnt1 and β-catenin Sourced from reference [14].

Note: A. Western blot detection of Wnt1 and β-catenin protein expression levels;
Quantitative analysis of Wnt1 and β-catenin protein expression; *P<0.05.

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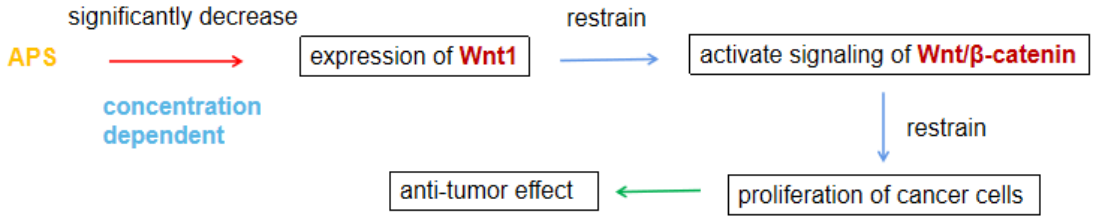

Figure 3. Diagram of APS anti-tumour mechanism.

3. Conclusion

This paper discusses the two signaling pathways that play a role in the treatment of cancer and myelosuppression, an adverse effect that occurs in the course of treatment, and finds that APS, the main bioactive ingredient extracted from the traditional Chinese medicine Astragalus, can play an vital role in reducing the expression of key genes, p53 and the ligand, Wnt1, and inhibiting the aberrant activation of the relevant pathways. At present, in the context of the urgent need to solve the problem of myelosuppression in chemoradiotherapy, it is particularly necessary to return to the classical theories of traditional Chinese medicine for inspiration, and then go deeper into the exploration of modern traditional Chinese medicine. However, this paper only focuses on two of the many complex pathways related to tumours, and there are still limitations and deficiencies in the further analysis of related pathways. At present, APS has been widely studied in clinical research, and many studies have been devoted to continue to advance its pharmacological mechanism in the face of many technical and methodological difficulties. In the future, research can pay more attention to the development of the combination of Chinese and Western medicines, in order to better complement each other's strengths and weaknesses, and to point out a new way out for clinical treatment means and medication guidance.

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