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The Adjuvant Potential of Astragalus Radix in Non-small Cell Lung Cancer Therapy

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Abstract. NSCLC is still a severe disease with high mortality in the whole world, which has threatened human life for a long time. The treatment of NSCLC are various and effective, however, with the prolongation of treatment cycle, the patients catch a lot of side effects and the tumor cells has developed mutations and drug resistance during the treatment. The traditional Chinese medicine can improve and alleviate this series of problems. This article talks about the pathogenesis, the external factor, symptoms and the relevant conventional therapy of NSCLC. It focuses on the analysis of the mechanism of Astragalus Radix (AR) as an adjuvant treatment from the perspectives of chemical composition and traditional Chinese medicine, and combined multiple cases and studies to analyze the advantages of combination therapy with AR compared with conventional therapy alone. Although the adjuvant treatment of AR is very effective, it still needs to be combined with other traditional Chinese medicine to form a compound preparation. This article also introduces two representative traditional Chinese medicine prescriptions containing AR and analyzes the additional adjuvant efficacy for NSCLC patients after using them in routine treatment. Finally, this article discusses and analysises the treatment efficacy of AR, the deficiencies in research and the limitation in NSCLC treatment of this herb to inspire the reseachers to find the potentiality of AR in NSCLC treatment.

Keywords: Astragalus Radix, NSCLC, adjuvant clinical treatment

1. Introduction

Cancer has developed as a prevalent and severe chronic disease worldwide. Among all types of cancer, carcinoma of the lungs has a quite high mortality rate, while the non-small cell lung cancer (NSCLC) is the most common sub-type in lungs, accounting for a significant portion of lung carcinoma cases. From the data that is collected in 2022, it shows that the lung cancer cases have reached a number of 2, 480, 675 and it accounts for 12.4% of new cancer cases worldwide [1]. The treatment of NSCLC are various and effective, such as chemotherapy, radiotherapy, biological therapy, targeted therapy etc. However, with the prolongation of treatment cycle, the patients catch a lot of side effects like vomiting, nausea, loss of appetite, fatigue etc., and the tumor cells has developed mutations and drug resistance during the treatment. Applying traditional Chinese medicine as an adjuvant therapy in clinical treatment can reduce the side effects of the conventional therapy. It can also significantly improve the patients' quality of life. Therefore, incorporating

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traditional Chinese medicine as an adjuvant treatment for NSCLC patients is a promising way. This article is going to talk about the role of Chinese herb AR in the treatment and adjuvant therapy of NSCLC.

2. Pathogenesis of non-small cell lung cancer

The Lung cancer is mainly divided into two types, one is small cell lung cancer (SCLC), another one is NSCLC. The NSCLC is named after the morphology of its cancer cells is checked under the microscopes, which is larger than the small cell lung cancer cells. Compared with SCLC, the growth and proliferation of this cancer is relative slow, thus the therapy of NSCLC is different from SCLC. The pathogenesis of NSCLC is multi factorial, involving a complex interplay of genetic, environmental, and lifestyle factors.

2.1. The etiology

The etiology of NSCLC is the same as the other cancer. The oncogenes such as EGFR, ALK etc., and tumor suppressor gene like p53, RB1 etc. have undergone mutations by various pathogenic factors in the lung cells, which causes the lung cells to proliferate abnormally. The variant cells escape from the surveillance of the body's immune system, which gives these abnormally proliferating cells chance to grow and develop into cancer in the lungs. With the development of NSCLC, the tumor will make incursions into another healthy tissues and even metastasize along the circulatory system or the lymphatic system.

In traditional Chinese medicine, the pathogenesis of NSCLC is not caused by a single factor. Instead, it is the result of the interaction and long-term accumulation between multiple factors, with deficiency of healthy Qi as the fundamental internal cause, and phlegm turbidity, blood stasis, and pathogenic toxins as the main pathological products and inducing factors. When the pathogenic toxins (such as wind-cold, wind-heat etc.) invade the lung, they will further consume healthy Qi and aggravate phlegm turbidity and blood stasis, as well as accelerating the accumulation of pathological products and eventually inducing NSCLC.

2.2. Common external pathogenic factor and symptoms

The common external factors of NSCLC are various. The most common external factor is cigarette, also the exposure of occupation, such as siliceous dust, chemical carcinogens etc. Additionally, the radiation and the chemical material are also worked as the factors causing the NSCLC. According to the research data, among the lung cancer patients, 75% of them smoke, while NSCLC accounts for 90.34% in the lung cancer [2]. In the early stage of NSCLC, the symptoms are the same as the common respiratory disease, which are therefore be ignored in patients' daily life.

The symptoms of NSCLC are mainly focused on lungs and respiratory tracts, for example, cough, shortness of breath, and if more serious coughing up phlegm, mucus or blood is quite common. When the tumor cells migrate to lungs or nearby areas, the symptoms like chest pain and hoarseness will present. NSCLC also has other symptoms on the patients, such as fatigue, loss of appetite, unexpected weight loss etc.

2.3. Common therapies of NSCLC

Nowadays, common clinical treatments for NSCLC include chemotherapy, radiation therapy, and targeted therapy. However, these treatment methods all have varying degrees of side effects, such as

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rash, weakened immunity, easy inflammation, diarrhea, nausea, decreased appetite, and even rare adverse reactions such as cardiotoxicity and anemia. This means that it is necessary to alleviate and eliminate adverse reactions and improve the quality of life of patients through several combination therapy methods. Assist treating NSCLC with traditional Chinese medicine is a novel and effective therapy, which has great research prospects. The patients with Yin deficiency constitution can use yin-nohrishing and fluid-generating herbs including Ophiopogon japonicus, Polygonatum odoratum, Hedyotis Diffusa. These components help patients reduce symptoms caused by fluid consumption [3]. Meanwhile, the patients who are lack of Qi can use qi-invigorating and body-strengthening herbs, such as AR membranaceus, codonopsis pilosula and so on [3]. This passage is mainly expand the discussion on the Chinese traditional herb AR in treating NSCLC.

3. The principle of AR in cancer treatment

The principle of AR in Cancer treatment can be analyzed from the perspective of traditional Chinese medicine and the activate chemical composition contained in AR.

3.1. Mechanism of AR in treating NSCLC from traditional Chinese medicine perspective

In the perspective of traditional Chinese medicine, NSCLC arises from the accumulation of pathogenic Qi in the lungs and the depletion of healthy Qi. The NSCLC is the result of the accumulation of positive feedback in disorder of metabolism. It is the fundamental internal cause of the healthy Qi deficiency in the lungs, the spleen and the kidneys, with the phlegm turbidity and blood stasis as the inducing factors raise the disorder of the body fluid metabolism. As a classical clinical Qi-replenishing medicine in traditional Chinese medicine, the AR belongs to the lung and spleen meridian. Meanwhile, the AR has relatively mild warmth, which can have nourishing and harmonizing effects. In clinical treating NSCLC as an adjuvant medicine, the AR play a role in enhancing resistance to the disease in body through strengthening and tonifying healthy Qi in lungs and spleen with other Chinese herb, so that it can relieve the symptoms of Qi deficiency such as shortness of breath and loss of appetite which are caused by NSCLC and the relative treatments. Additionally, the astragalus can work with other herbs to upright the healthy Qi to reduce the damage from pathogenic factors to the body.

3.2. Analysis of the mechanism of action by the active ingredients of AR in treating NSCLC from the perspective of chemical composition

There are several kinds of majority components of the AR. Their effective active ingredients are shown in Table 1.

Table 1. The main active ingredients of AR

Type of active substance	Specific components	Main functions
Polysaccharides	Astragalus Polysaccharides	Immune regulation, antioxidant activity, anti-tumor effect, etc.
Saponins	Astragaloside IV, Astragaloside I, Astragaloside II, Astragaloside III, etc.	Antioxidant activity, anti-aging effect, metabolic regulation, immune regulation, etc.
Flavonoids	Formononetin, Calycosin, Isoliquiritigenin, etc.	Participate in in vivo metabolism

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Table 1. (continued)

Amino Acids	Proline, γ-Aminobutyric Acid (GABA), etc.	Participate in in vivo metabolism
Trace Elements	Iron (Fe), Zinc (Zn), Selenium (Se), Copper (Cu), etc.	Assist in maintaining physiological functions

3.2.1. Astragalus Polysacchride (AP)

The research result from Shan, X.F. based on the clinical analysis of 68 cases of advanced NSCLC case shows that the therapeutic effict of the control group combination chemotherapy plan with Carilizumab and Albumin-bound paclitaxel plus carboplatin (TP) is not as efficient as that of experimental group on the basis of the treatment plan in control group, in which the AP was added [4]. The Pharmacological studies have found that AP has various functions such as henhancing the body's immune system, improve patient tolerance, and it can also enhance cell activity maintain the structure of normal cells [5]. The AP can activate the apoptosis signals of NSCLC cells by down-regulating the expression of anti-apoptosis proteins and up-regulating the expression of pro-apoptosis proteins to promote the apoptosis of the tumor cells, moreover, it can interfere with the cell cycle to stagnate the cells in the G0/G1 phase, leading to inhibit the tumor progression [6].

3.2.2. Astragaloside IV (AS-IV)

Current clinical conclusions regarding AS-IV are still in the research stage, the relevant research are in the field of network pharmacology. The human lung A549 cell line is a type of NSCLC, and it is a commonly used cell model in NSCLC research. In the mechanism of A549 resistant to cisplatin (DDP) model (A549/DDP cell), it can occur that the protective cellular autophagy can be induced by DDP, so that the cell line can resistant to the apoptosis induced by DDP. The result of network pharmacology from Li, Z.R. shows that the AS-IV can reduce the resistance of A549/DDP cell by inhibiting the excessive cellular autophagy mediated by PI3K/AKT/mTOR signaling pathway induced by DDP, bring about enhancing the sensitivity to DDP, and improving the efficacy of DDP [7]. AS-IV can also enhance the sensitivity of NSCLC to bevacizumab via the lnc RNA-PVT1/miR-361-3p/HMGB1 axis [8].

4. The therapeutic advantages of AR in adjuvant treatment of NSCLC

In treating NSCLC, the AR as an adjuvant treatment the advantages are numerous and remarkable.The AR combined with common treatment as adjuvant therapy for NSCLC and other tumors has the core advantages of enhancing efficacy, reducing toxicity, improving the body condition, and compensating for the limitations of common treatment alone. The platinum-based drugs can cause the side effects during the chemotherapy to the NSCLC patients, for example, bone marrow suppression, gastrointestinal reactions, liver and kidney function damage. The monoclonal antibodies (mAb) may cause immune related adverse reactions, infusion reactions, fatigue, etc, while the targeted drugs can easily cause rash, diarrhea, oral ulcers, liver and kidney function damage, etc [9]. However, the AR are able to enhance patient tolerance by regulating the immune system balance and protecting organ functions to reduce leukopenia, nausea and vomiting etc, and it can reduce the probability and severity of occurrence, in order to improve the patient medication adherence.

Moreover, some of the NSCLC cells are resistant to the platinum based drugs with the chemotherapy period longer, while AR-IV and AP can obstruct the self-protective of these tumor

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pathway and improve the sensitivity of the immune system to inhibit the resistance of the drug resistant cells in order to improve the efficacy of the chemotherapy. With the sensitivity of immune system improving and the activity of the immune cells being activated, it can complement the targeted action of mAb to improve the clearance efficiency of tumor cells and prolong the duration of therapeutic effect. If the targeted therapy are implemented alone for a long period, the tumor resistance is prone to occur [9]. The immune regularity of the AR can assist in inhibiting the escape mechanism of tumor cells, form synergy with targeted drugs to prolong the effective time of drug action, and delay the occurrence of drug resistance.

Finally, the AR can nourish the healthy Qi and blood, it can also improve energy metabolism of the patents' body, so that it can help the patients improve the nutritional status and maintain the bodily functions. It can significantly reduce the decline in quality of life result from fatigue, decreased appetite, and decreased physical strength often caused by the disease, the chemotherapy, mAb therapy and targeted therapy.

5. Compound Chinese medicine containing the Chinese medicine and their respective functions

5.1. Fangji Huangqi Soup

Fangji Huangqi Soup comes from Synopsis of the Golden Chamber written by Zhang Zhongjing of the Han Dynasty. The composition of the prescription is that 12g Fangji, 15g Huangqi (AR), 9g Baizhu (Atractylodes macrocephala Koidz), 6g honey-fried licorice root, 4 slices of ginger and 12 jujubes. The core function of Fangji Huangqi soup is nourishing healthy Qi, strengthening spleen, promoting diuresis, and dispelling dampness. Therefore, the soup can assist the patients in regulating the deficiency of healthy Qi and the excessive of dampness, in addition, it can also restore spleen and stomach function and physical strength to ameliorate the physical function of the patient who caught the symptoms such as physical weakness and cessation of dampness after the NSCLC treatment like chemotherapy and radiotherapy. The research from Cao H.S. shows that Fangji Huangqi soup is helpful with lung function recovery to the patients after lobectomy by helping the body improve immune function and alleviate lung ischemia-reperfusion injury caused by surgery [10]. Moreover, the soup can not only inhibit the maturity of acidic hydrolytic enzymes in autolysosomes to retard the late stage autophagic in NSCLC cells, but also promote the accumulation of ROS in NSCLC and further activate the ROS-MAPK pathway with DDP and paclitaxel [11].

5.2. Danggui Buxue Decoction

The composition of the prescription is that 30g Huangqi (AR) and 6g Danggui, and compatibility of other herbs based on the patient's physical characteristics. For example, the individuals with the deficiency of healthy Qi and blood, and phlegm stasis nodules can use thunberg fritillary bulb, spica prunellae and raw oyster shell in addition to achieve the goal of replenishing blood, nourishing Qi, resolving phlegm, and dispersing nodules. The core function of Danggui Buxue Decoction is improve the symptoms like fatigue, pale complexion, dizziness, palpitations, shortness of breath, and spontaneous sweating in patients, especially suitable for the cases of bone marrow suppression and blood and healthy Qi depletion after the chemotherapy and radiotherapy. Liu, Y. C., Xu, F. et al. found that the decoction can release the side effect bone marrow suppression after chemotherapy and it can also inhibit the proliferation and metastasis of the tumor cells and enhance the function of

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immune system by inducing A549 apoptosis and increasing the content of granulocyte-macrophage colony-stimulating factor (GM-CSF) [12].

6. Discussion

Nowadays, NSCLC therapies accurate stage in medical treatment field. The treatment methods are not only chemotherapy, radiotherapy, biological agents but also the traditional Chinese medicine as the adjuvant treatment. The AR is a typical traditional Chinese herb as an adjuvant medicine in NSCLC therapy. It is beneficial to the healthy Qi and blood, improve the immune system, strengthening the lungs and spleen, and also plays an important role in inhibiting the self-protection autophagy of tumor cells to reduce their resistance to drugs that induce apoptosis such as DDP and promoting the tumors apoptosis. The active substances contained in the AR are various and different ingredients can have different efficacy, therefore some of the special ingredients are extracted and researched alone such as AP, AS-IV etc. These active substances can obstruct the NSCLC cell cycle in G0/G1 stage and stop the tumors proliferation and metabolism. With other traditional Chinese medicine, the compound preparation can utilize the advantages of different traditional Chinese medicines and achieve a positive anti-cancer effect in combination with conventional therapies. For example, the Fangji Huangqi soup can nourish healthy Qi, strengthen spleen, promote diuresis, and dispel dampness of the body.

However, the ingredients of herbs are complex, the role of some components in AR has not been fully and clearly studied. While the core function of AR is invigorating healthy Qi and strengthening spleen, it can not directly inhibit or kill NSCLC cancer cells, or replace standard treatment such as surgery, radiotherapy and chemotherapy. Meanwhile, the AR can only effective to the patients who have deficiency of healthy Qi and blood and insufficiency of the spleen. If the patient has yin deficiency and internal heat or bleeding tendency, using AR mistakenly will make the condition of the patients more serious. Therefore, using AR reasonably, dialectically and base on patients' own symptoms and exploring more efficacy of AR in adjuvant treatment of NSCLC should be further explored.

7. Conclusion

This article is focusing on the pathogenesis, the external factor, symptoms and the relevant conventional therapy of NSCLC. NSCLC is caused by the variation of the lung cells and the immune escape of these mutant cells, which let the cells get chances to develop into NSCLC. It focused on the analysis of the mechanism of AR as an adjuvant treatment from the perspectives of chemical composition and traditional Chinese medicine, and combined multiple cases and studies to analyze the advantages of combination therapy with AR compared with conventional therapy alone. In chemical composition, the functions of AR ingredients such as AP and AS-IV are illustrated. The AP can activate the apoptosis signals of NSCLC cells to promote the apoptosis of the tumor cells and can interfere with the cell cycle to stagnate the cells in the G0/G1 phase, leading to inhibit the tumor progression, while the AS-IV can inhibit the excessive cellular autophagy mediated by PI3K/AKT/mTOR signaling pathway to reduce the resistance of DDP in A549 cell. It is clearly showed that the combination therapy with AR can improve the efficacy of the therapies, reduce the resistance of some tumor cells and extend the effective time of treatment. Although the adjuvant treatment of AR is very effective, it still needs to be combined with other traditional Chinese medicine to form a compound preparation. Fangji Huangqi soup can inhibit the maturity of acidic hydrolytic enzymes in autolysosomes to retard the late stage autophagic in NSCLC cells, and

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promote the accumulation of ROS in NSCLC and further activate the ROS-MAPK pathway with DDP and paclitaxel, while Danggui Buxue decoction can inhibit the proliferation and metastasis of the tumor cells and enhance the function of immune system by inducing A549 apoptosis and increasing the content of GM-CSF. As an adjuvant therapy, there are still many research gaps still in exploration. This article also aims to provide a reference for the application of AR as an adjuvant in the treatment of NSCLC.

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