Adjuvant Effects of Natural Products of Herbal Origin in Tumor Therapy and Their Mechanisms

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Abstract. Cancer has always been a major obstacle to people living a healthy life. How to treat cancer and reduce the sequelae of treatment is one of the key research projects today. The majority of cancer treatments still use a combination of surgery and chemotherapy, which is costly and prone to a range of adverse effects and complications. It is urgent to find new treatment options and to alleviate patients' adverse reactions. This paper studied several typical natural products and found that plant extracts have more obvious positive effects in inhibiting tumor angiogenesis and slowing down the side effects of surgery. The use of such natural extracts can effectively inhibit the cancer therapy-induced sequelae, improve the lives of patients. In addition, some plant extracts also have a good inhibitory effect on the growth and spread of cancer cells. These natural products can be used as specific in the treatment of cancer, effectively reducing tumor cells and inhibiting their rate of spread.

Keywords: Cancer, Ginsenoside, Artemisinin, Lignans, Paclitaxel.

1. Introduction

Cancer has long been known as a major medical challenge due to its high mortality rate and difficulty in treatment. The incidence and mortality rate of cancer is gradually increasing worldwide. According to statistics from the GLOBOCAN (The Global Cancer Observatory) project of the International Agency for Research on Cancer (IARC) of the World Health Organization in 2020, only in that year, there were more than 19.3 million cancer cases all over the world, worse still, more than 10 million people died of cancer. Lung and prostate cancers are the most common cancers in males, while breast cancer has overtaken lung cancer as the most common cancer in females. According to the agency's forecasts, the number of cancer patients is expected to grow by more than 40% globally by 2040, with the proportion expanding further in regions of the world where the HDI (Human Development Index) is even lower. The rate is likely to increase further due to factors such as globalization and economic growth.

At present, the most frequently used cancer treatment options include surgical resection, radiotherapy, chemotherapy, targeted drug therapy, immunotherapy, etc. Among them, the most common one is the combination of surgical treatment and chemotherapy and radiotherapy, which is highly recognized. However, because tumor cells are difficult to be completely removed, for some cancers, minimally invasive surgery carries a certain risk of recurrence. Cancer patients often require multiple surgeries, who were difficult to eradicate the disease. In recent decades, the use of natural herbal extracts for adjuvant cancer treatment has gained more attention. Many researchers have suggested that the use of plant-derived natural products as an adjunctive treatment option to conventional therapies can greatly alleviate the shortcomings of conventional therapies. Not only that, but some plant extracts have also been found to have effects such as inhibiting tumor angiogenesis and inducing autophagic death of tumor cells. The goal of this paper is to focus on the adjuvant effects of herbal extracts in cancer therapy with a focus on common plant natural products.

2. Ginsenoside

2.1. ginsenoside basic structure

The often-mentioned herb ginseng refers to the tuberous root of Panax ginseng C. A. Meyer. Ginseng has been used as a complementary medicine in Eastern countries for thousands of years, mainly for toning the body and fighting fatigue [1]. Modern scientific research has confirmed that ginsenosides (also called triterpene saponins) are the main active ingredients in ginseng. Lu JM, Yao Q and Chen C et al. have extracted more than 100 active ingredients from ginseng [2], after compositional analysis, ginsenoside Rg3 was shown to have significant physiological activity.

One of the most important ginsenosides is ginsenoside Rg3, which is a tetracyclic triterpenoid saponin. Ginsenoside Rb1, ginsenoside Rb2 and ginsenoside Rd can be converted to ginsenoside Rg3 through a series of transformations. Meanwhile, its conversion is further enhanced under heating conditions (from 0.37% to 1.32% (w/w)) [3].

According to the orientation of the hydroxyl group at the C-20 position in ginsenoside, it is divided into 20(S) and 20(R), which are isomers of each other. Two different conformations of ginsenoside Rg3, 20 (S) and 20 (R), were obtained by adsorption chromatography, silica gel partition chromatography, recrystallization and preparative HPLC fractionation (Figure 1) [4]. These two conformations differ in their tumor cell inhibitory activity. Generally, 20(S) compounds have better inhibitory effects on tumor cell proliferation, while 20(R) compounds are more effective in slowing down the spread and metastasis of tumor cells [5].

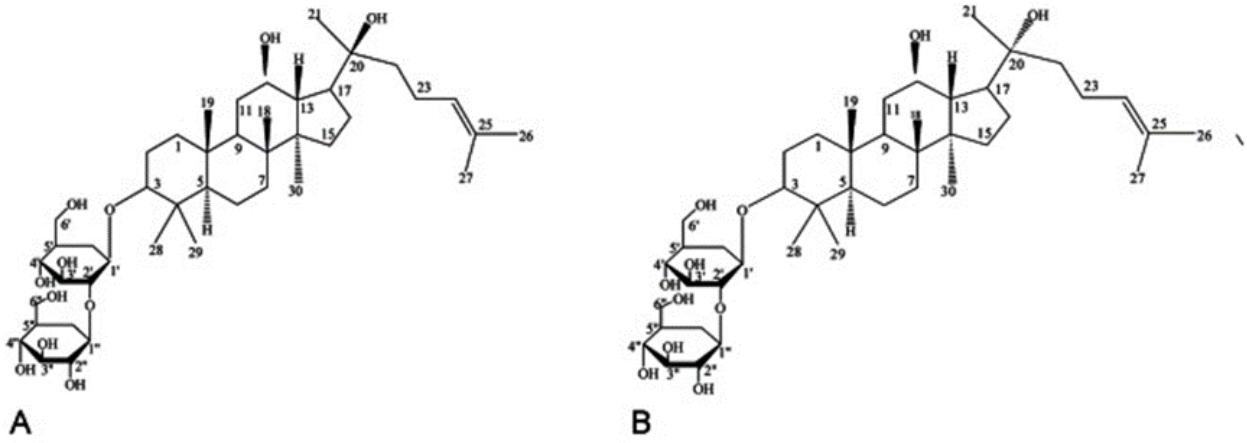

Figure 1. Chemical structures of (20S)-ginsenosides Rg3 (A) and (20R)-ginsenosides Rg3 (B) [4].

2.2. Adjuvant effects of ginsenosides on tumor treatment

TAE (Transcatheter arterial embolization) is a common minimally invasive procedure for the treatment of tumors [6], which can be used to improve the QOL (quality of life) and increase patient survival [7]. However, TAE might induce ischemia and hypoxia in tumor cells, thus stimulating tumor angiogenesis [8], which ultimately accelerates cancer cell replication and promotes tumors to metastasize. Although TAE is convenient and effective in treating tumors, there is a risk of tumor recurrence.

Kim et al. demonstrated that the combination of chemotherapy with Rg3 can enhance its therapeutic effect and reduce its side effects [9]. YU Y et al. investigated three treatment options (Rg3 drug therapy, TAE alone, and TAE combined with Rg3) for VX2 liver tumors in rabbits. By Immunohistochemistry and western blot analysis they found that TAE combined with Rg3 was more effective in the treatment of rabbit VX2 liver cancer [10].

Rg3 is effective in various aspects such as inhibition of tumor cell proliferation and metastasis, promotion of tumor cell apoptosis and enhancement of patient immunity. However, there is a little lack of clinical application of Rg3 in combination with TAE due to the immaturity of the currently available studies.

3. Artemisinin derivative

3.1. Artemisinin derivatives

The most famous of the Artemisia plants is Artemisia annua Linn., from which Chinese scientist Tu Youyou extracted artemisinin. Currently, Artemisinin is the most effective drug for the treatment of malaria. Artemisinin is a sesquiterpene lactone. Inserting the new groups into artemisinin can get a series of artemisinin derivatives. These derivatives have anti-tumor effects. Typical representatives of these are artemisinin (ART), artemether (ARM), artesunate (ARS) and dihydroartemisinic (DHA) (Figure 2).

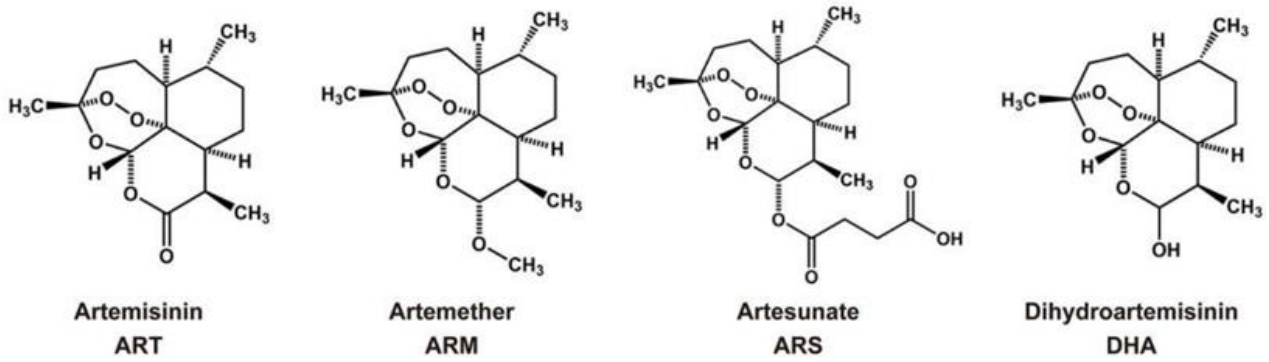

Figure 2. Chemical structure of ART, ARM, ARS and DHA [11].

3.2. Inhibition of cancer cell proliferation by artemisinin derivatives

By investigating the effects of artemisinin derivatives on cancer-associated fibroblast activity, ARS and DHA were found to be able to inhibit the Transforming Growth Factor-β (TGF-β) signal pathway. This causes CAFs to change from an activated state to an inactivated state. CAFs can release growth factors and cytokines into the blood circulation, leading to proliferation of tumor cells and angiogenesis. By inhibiting the expression of TGF-β, it can effectively suppress the production of CAFs and ultimately achieve the effect of inhibiting the proliferation of cancer cells [11].

3.3. Effect of artemisinin derivatives on autophagy of cancer cells

The most important artemisinin derivative is DHA, which has been used as an anti-cancer agent. Like most artemisinin derivatives, DHA is chemically poisonous to cells and is involved in the regulation of several physiological activities such as apoptosis, autophagy, cell cycle arrest, reactive oxygen species (ROS) generation, and participation in the Th1 immune response shift. For cancer cells, DHA has a higher Chemical toxicity, but for normal cells its toxicity is relatively lower [12]. This Chemical toxicity allows DHA to participate in cell autophagy and induce cancer cell death [13].

In addition to DHA, ART can also cause autophagic death of cancer cells. By studying the effect of ART in the autophagic death of breast cancer cells, Chen K et al. found that ART can induce G2/M cell cycle arrest in breast cancer fine, which leads to a substantial increase in the cell cycle protein Beclin1 and apoptosis of breast cancer cells, ultimately leading to autophagic death of breast cancer cells [14].

4. Lignans

4.1. Lignans

Lignans are diphenolic compounds containing 2,3-dibenzylbutane (The structure is formed by the dimerization of two cinnamic acid residues) [15]. Lignans are widely found in vegetables and fruits as well as in cereals, and the best sources of lignans are flaxseed and flour at present.

Lignans were first discovered due to their good digestive regulation, of which the two most significant types are metaraminol (MAT) and secoisolariciresinol (SEC) (Figure 3). Estrogen is an

important hormone for the growth and differentiation of important tissues in the human body (especially the breast and prostate) and has always played an important role in the growth and development of the body. Magee PJ et al. found that estrogen not only regulates the growth and development of human tissues, but is also associated with the growth and spread of cancer when they studied the physiological activity of estrogen. Because the structure of lignans is similar to 17-β estradiol, the effect of lignans on estrogen-mediated pathways has been investigated.

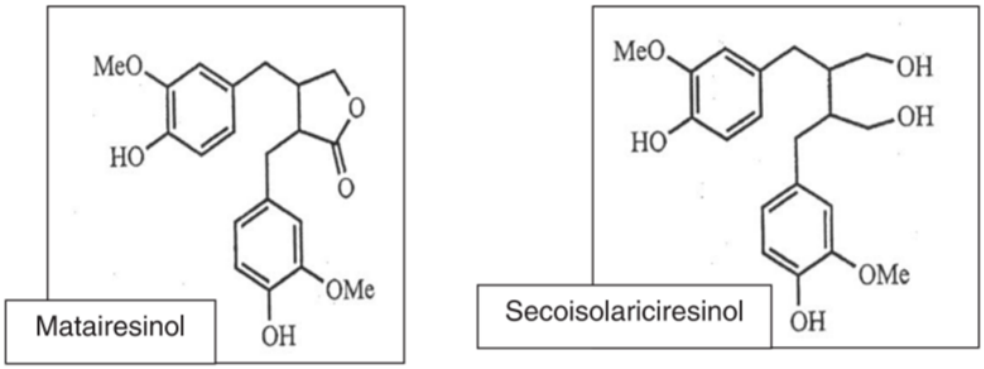

Figure 3. Chemical structure of MAT and SEC [16].

4.2. Effect of lignans on VEGF

Compared to normal cells, cancer cells tend to require more nutrition due to their unrestricted growth and division. Not only this, but tumor cells need a lot of nutrients to support when they are spreading. The supply of nutrients through the blood vessels is the body's primary way of transferring nutrients. Tumor cells are the same as this. In order to invade normal tissues, cancer cells need to spread and thus pass to various parts of the body. Therefore, tumor cells need to form a large number of tumor blood vessels to ensure sufficient nutrient supply in the process of proliferation and spread.

VEGF (vascular endothelial growth factor) is derived from endothelial cells in hypoxic conditions. Tumor cells in a hypoxic state will stimulate VEGF production, thus promoting tumor angiogenesis [15]. As a result, reducing VEGF concentration can effectively inhibit tumor blood vessel formation and thus achieve tumor suppression.

By researching the effect of flaxseed diet on extracellular VEGF concentrations, Dabrosin et al. found that the active ingredients in flaxseed (especially lignans) were able to reduce VEGF concentrations through two pathways: the estrogen indirect-dependent pathway and the estrogen non-dependent pathway [17].

Due to the estrogen response element (ERE) possessed by VEGF that binds to the estrogen receptor and is transcriptionally regulated by gene sequences Lignans are able to participate in estrogen-mediated pathways leading to a decrease in estrogen, so that less estrogen is able to bind to VEGF-ERE, thus affecting VEGF production.

5. Paclitaxel

5.1. Paclitaxel

Naturally occurring in the tree bark and coniferous of Taxus wallichiana var. chinensis, paclitaxel is a tricyclic diterpenoid with the molecular formula $C_{47}H_{51}NO_{14}$ (Figure 4). Paclitaxel, as a natural anti-cancer drug, has its own unique anti-cancer mechanism. It is called one of the most successful and widely used natural anti-cancer drugs available [18]. In 1992, the FDA (U.S. Food and Drug Administration) had already approved the use of paclitaxel for the treatment of ovarian, breast and lung cancers and Kaposi's sarcoma [19].

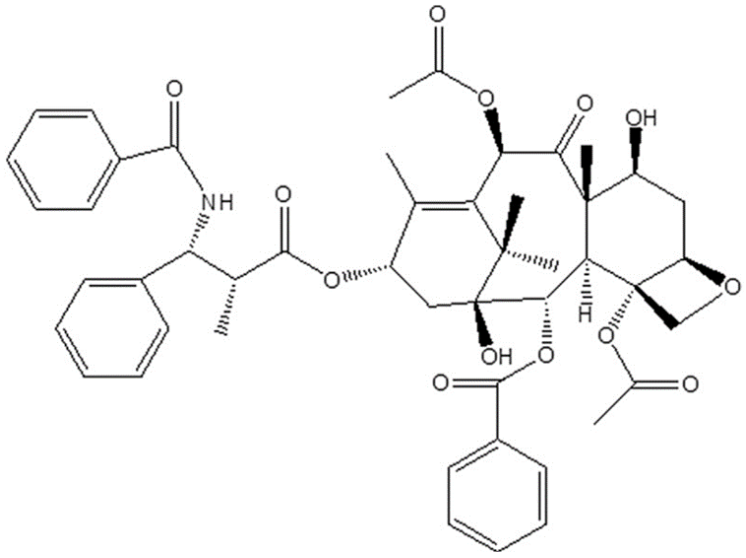

Figure 4. Chemical structure of Paclitaxel.

5.2. Anti-cancer mechanism of paclitaxel

Paclitaxel is a kind of cytotoxic anti-tumor drug with special mechanism of action. Its anti-tumor effect is mainly reflected in the ability of paclitaxel to act on microtubule proteins and microtubule system as well as the regulation of the immune system. Jordan et al. found that high concentrations of paclitaxel bound to tubulin resulted in a substantial upregulation of the number and rate of formation of microtubule dimers through experiments. Tubulin dimers assemble into microtubules and aggregate, thereby promoting the formation of microtubule fasciculus. This disrupts microtubule reorganization and ultimately effectively blocks mitosis and abnormal cell proliferation [20].

In clinical research, paclitaxel has been found to have significant physiological activity against breast and ovarian cancers. However, because the physiological activity of paclitaxel is not limited to cancer cells but affects the entire microtubule system, it is toxic to all cells in the body. This causes paclitaxel to have a variety of side effects such as allergic reactions, joint pain, gastrointestinal discomforthair, hair loss and so on. These side effects seriously affect the use of paclitaxel in clinical applications.

6. Conclusion

In this paper, herbal extracts were found to play a positive effect in the adjuvant treatment of cancer. The addition of herbal extracts as an adjuvant after cancer treatment is beneficial in mitigating adverse effects and complications compared to conventional monotherapy. This can effectively alleviate various adverse reactions caused by anti-cancer therapies, reduce the incidence of complications, and decrease the rate of tumor recurrence, etc. In addition, some natural drugs have been shown to have cytotoxic activity to induce autophagic death of cancer cells, and such drugs could be effective agents involved in the treatment of cancer. In summary, natural medicine is suitable as an adjunct to cancer treatment and provides an effective way to fight and cure cancer in addition to traditional treatment options.

Despite many advantages of herbal extracts as an adjunct to the treatment of cancer, current research has significant limitations: As a natural medicine, the current research focuses more on its efficacy and function, while there is still a large degree of gap in the efficient extraction and synthesis of active ingredients of herbal medicines; The research on many herbal extracts is still limited to the more superficial level, and there is a lack of exploration of the deeper molecular mechanisms. In summary, future research should focus more on finding more effective herbal extracts and digging deeper into their pharmacological essence to provide strong support for potency improvement and cancer treatment applications.

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