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Progress in the Use of Natural Products for the Treatment of Lung Cancer

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Abstract: Lung cancer is a malignant disease with high morbidity and mortality, which affects the quality of life of patients. It has become one of the most serious public health problems in the world. Most natural products have a variety of anti-tumor activities. In recent years, scholars at home and abroad have studied the anti-tumor effect and mechanism of natural products from many aspects, especially in lung cancer. In this paper, the review on the active components of natural products in the treatment of lung cancer will provide a basis for subsequent treatment of lung cancer.

Keywords: Natural products; Lung cancer; Active components

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1. Introduction

Malignancy has been one of the major causes that threaten the lives of residents. It is and will be one of the great challenges in the medical community in this 21st century and in the future. In China and even across the world, the incidence and mortality of lung cancer have ranked first for a long time [1]. According to the 2021 Global Cancer Report, the number of new lung cancer cases was 2.1 million, which had led to 1.8 million deaths [2]. Due to China's developed heavy industry and other factors leading to air pollution, the incidence of lung cancer in China is much higher than the world's average [3,4]. Therefore, treating lung cancer is one of the issues faced by the medical field in China at the present stage.

At present, surgery is the main way to completely eradicate lung cancer, but some lung cancers have already metastasized at an early stage [5]. The probability of relapse is also extremely high in lung cancer. Chemotherapy is one of the most commonly used methods in the treatment of lung cancer [6]. However, existing clinical broad-spectrum chemotherapeutic drugs generally have serious side effects [7]. Therefore, it is urgent to explore for a novel anti-tumor drug with low toxicity but with high efficacy.

In recent years, research has been focusing on natural products. The anticancer effect of natural products derived from herbs, fungi, or marine organisms have been studied to overcome the issues encountered in the treatment of cancer [8]. It has been discovered that about 60% of anticancer drugs come from natural products [9]. Natural products are characterized by low toxicity and side effects. There are reports on the use of natural drugs to treat liver cancer [9], osteosarcoma [10], and other cancers, with positive outcomes. Therefore, this paper summarizes the recent research on the use of natural products in the treatment of lung cancer to explore their therapeutic effects on lung cancer.

2. Paclitaxel

Paclitaxel is a secondary metabolite – diterpenoid alkaloid – extracted from yew. It is widely used for cancer.

As the first approved natural anticancer drug in the FDA, it has a long history. It has played a major role in the treatment of cervical cancer, breast cancer, lung cancer, and other cancers [11-13]. Paclitaxel was first reported in 1993 to be active against advanced non-small cell lung cancer, and it was found to considerably increase the median survival in patients [14]. Lung cancer patients were reported to have a greater in vitro sensitivity to paclitaxel than cisplatin [15]. However, paclitaxel can be safely used in combination with cisplatin. Eighty patients with advanced non-small cell lung cancer were selected in a study to investigate the effects of using paclitaxel and cisplatin [16]. The results found that both $CD4^+$ and $CD4^+/CD8^+$ levels were elevated in the combination-treated group, thus improving their immunity. Moreover, the adverse effects experienced by the combination-treated group were far lesser than those of the two drugs administered separately, indicating that it can significantly improve patients' quality of life.

While paclitaxel is used to treat cancer, people also tend to focus on its gastrointestinal effect, myelosuppression, allergic reaction, and other side effects [17]. Its side effects are likely to contribute to a discontinuation of treatment or treatment failure. The transport of paclitaxel via liposomes can prevent various side effects. Researchers have encapsulated paclitaxel in two different sizes of cationic liposomes (180 to 200 nm and 80 to 100 nm), in which good biocompatibility and anti-tumor effects have been observed in A549 non-SCLC. Through in vivo experiments, paclitaxel incorporated liposomes were reported to reduce tumors in nude mice quicker than paclitaxel alone. No mechanical or thermal allergies were caused [13]. In order to better promote the delivery of chemotherapeutic drugs to lung tumors, chitosan oligosaccharide modified liposomes were introduced to encapsulate paclitaxel, showing a stronger effect in A549 cells in vitro [18]. Paclitaxel is one of the important drugs for lung cancer in clinical practice.

3. Usnic acid

Usnic acid was first discovered as a secondary metabolite with anti-tumor activity. Songluo is a traditional Chinese medicine with high medicinal value and is known to have more than 1,000 secondary metabolites [19]. Most of its active ingrdients play a significant role in the treatment of lung cancer, especially usnic acid. Usnic acid has an inhibitory effect on the growth of human lung cancer cells [20,21]. The growth and cell cycle of lung cancer cells are also affected. The proliferation of A549 cells is suppressed 24 hours and 48 hours following the addition of usnic acid at different concentrations, in which cells are blocked in the G0/G1 phase during both time periods, and CDK4, CDK6, and cyclin D1 are affected [22,23]. It inhibits proliferation while promoting apoptosis in cancer cells. A study discovered that usnic acid can induce the production of reactive oxygen species (ROS) by inhibiting the mitochondrial respiratory chain (MRC) complex I and complex III, which induces mitochondria and disrupts the PI3K/Akt pathway, thus lowering Nrf2 stability (ROS) [24]. The accumulation of reactive oxygen species reduces the viability of lung SCC cells and induces apoptosis. The role of usnic acid in lung cancer has been validated in numerous experiments, but its mechanism has not been fully understood. Therefore, it is critical to continue the investigation.

4. Crocin

Crocin is one of the bioactive compounds extracted from saffron, which is commonly used in the treatment of spasticity, asthma, liver disease, and cancer [25]. Research has shown that crocin is a TMEM16A ion channel inhibitor, and a high endogenous expression of TMEM16A ion channel in lung cancer is closely related to lung cancer cell proliferation and migration [26]. It has been discovered that crocin inhibits proliferation and migration of LA795 and NCI-H1299 in lung cancer cells by inhibiting TMEM16A. Crocin has a substantially lower inhibitory effect on LA795 cell proliferation and migration when TMEM16A expression is reduced intracellularly [27]. Crocin suppresses lung cancer cell proliferation and induces apoptosis [28]. It is concentration-dependent in A549 and SPC-A1 cells, along with an increased G0/G1

phase arrest. Crocin can significantly increase the mRNA levels of p53 and Bcl-2-associated X protein (BAX) and reduce the mRNA expression of B-cell lymphoma 2 (Bcl-2). In addition, the combination of saffron with cisplatin has an additive effect on the cell growth inhibition rate in the two lung cancer cell lines [29]. Crocin can be studied as a lead compound in the development of lung cancer therapies.

5. Ecliptasaponin A

Ecliptasaponin A (ES) has potent anticancer properties in a variety of cancer cells, especially lung cancer. In non-small CLC, ES inhibits H460 and H1975 proliferation, with a dose-response relationship. It suppresses migration and invasion-related proteins (E-cadherin, N-cadherin, and Vimentin) as well as cycle-related proteins (Cyclin D1, CDK6, and P21) in non-small cell lung cancer [30]. It also induces apoptosis and autophagy in both cancer cells, while inducing apoptosis in human lung cancer cells by the ASK1/JNK pathway, apoptosis-related proteins (cleaved caspase 8, cleaved caspase 9, cleaved caspase 3, BAX, and Bcl-2) as well as autophagy-related proteins (LC3a/b, beclin-1, and p62) [30,31]. ES is most likely a promising therapy for lung cancer.

6. Silybin

Silybin is a phenolic flavonoid isolated from thistle. It plays a major role in the treatment of tumors. Silybin inhibits the proliferation, migration, and invasion of various non-small cell lung cancer cells (A549 cells, H1299 cells, and LLC cells) by acting on the Skp2/P27 pathway [32]. The mRNA and protein expressions affecting Capase-3, Caspase-9, and Bcl-2 promote apoptosis in A549 cells [33]. Tumorigenesis and development are regulated by inhibiting PD-L1 expression in lung cancer cells [34]. In a lung cancer mice model, silybin was administered intraperitoneally. At 400 mg/kg, good anti-tumor activity was seen without any renal or hepatic toxicity [32]. It can be deduced that silybin is a compound with low toxicity and minimal side effects for lung cancer.

7. Conclusion

Researchers at home and abroad have confirmed through various investigations that the active components of natural products can affect the multiple links of lung tumor development and metastasis, but there are only a few clinical and mechanism reports. Therefore, further discussions are required in these fields. It is of great significance to investigate the diversity of active components found in natural products for the treatment of lung cancer. This paper provides a direction in the search for new active ingredients and the clinical development of new drugs.

Disclosure statement

The authors declare no conflict of interest.

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