CHAPTER 31

Therapeutic Potential of Medicinal Plants in Non-Small Cell Lung Cancer (NSCLC)

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SUMMARY

Non-small cell lung cancer (NSCLC) is a major health concern, accounting for 85% of all lung cancers. Current treatment options for non-small cell lung cancer include surgery, chemotherapy, radiation and newer approaches like targeted therapy and immunotherapy. Now a days, there is a growing interest in traditional herbal medicine that offers a complementary approach to these conventional therapies in the treatment of cancer. Plants and their extracts have shown promise in lung cancer treatment by improving the effectiveness of conventional treatments, extending patient survival, reducing side effects and enhancing quality of life. This chapter discusses the potential of medicinal plants as a natural source of anti-cancer agents for treating non-small cell lung cancer (NSCLC). It will explore a range of plants currently under investigation and their encouraging results in lung cancer management.

INTRODUCTION

Among different types of cancers, lung cancer is the leading cause of cancer-related deaths. Lung cancer arises from the uncontrolled growth of abnormal cells within the lungs. This cancer is mainly divided into two types based on the morphology of cancer cells. Non-Small Cell Lung Cancer (NSCLC), which accounts for roughly 85% of all lung cancers and Small Cell Lung Cancer (SCLC) which makes up the remaining 15% (Travis et al., 2015). NSCLC can be further categorized into three main histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

Adenocarcinoma, the most prevalent form, affecting roughly 40% of NSCLC patients, often originates in the bronchioles, the lung's tiny airway branches. Adenocarcinoma can occur in both smokers and non-smokers. Additionally, it tends to progress slowly, that potentially allows for earlier detection and treatment. The World Health Organization (WHO) categorizes lung adenocarcinomas into different subtypes, including lepidic, acinar, papillary, solid, and micropapillary adenocarcinomas based on their histological characteristics (Hutchinson et al., 2019). The second most common subtype of NSCLC is squamous cell carcinoma (SCC), which is also known as epidermoid carcinoma. It accounts for roughly 25-30% of diagnosed cases. As the name suggests, SCC arises from the squamous cells lining the airways, the thin, flat cells that give it its name. This type of lung cancer exhibits the strongest association with smoking compared to other NSCLC subtypes (Takamochi et al., 2016). Large cell (undifferentiated) carcinoma is very rare and it accounts for only 10% of NSCLC. This form of NSCLC is the hardest to treat as it is very aggressive and can form anywhere in the lungs. Large cell cancers account for approximately 5-10% of all lung cancers. These tumors are typically poorly differentiated and composed of large cells with abundant cytoplasm and large nucleoli.

The classification of lung cancer is a dynamic field, with ongoing refinements in terminology and criteria to differentiate subtypes, especially in poorly defined tumors. This growing precision is crucial as targeted therapies emerge for specific lung cancer subtypes. Previously unclassifiable tumors can now be re-evaluated through differential diagnostic studies that potentially lead to more effective treatment options. The prognosis for NSCLC is significantly impacted by the stage of diagnosis, while early-stage disease offers better outcomes (68% five-year survival rate for stage IB). Survival rates decline sharply in later stages i.e. 0-10% for stage IVA-IVB (Goldstraw et al., 2016). Smoking is the undisputed leading risk factor for lung cancer. Exposure to

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other carcinogens like asbestos and ionizing radiation also plays an important role (Kirk et al., 2007). Additional risk factors include a history of pulmonary fibrosis, HIV infection and alcohol consumption. Unfortunately, inadequate screening programs and late presentation of symptoms often result in advanced-stage diagnoses, leading to poorer prognoses.

The lack of clear symptoms in early stages and the absence of widely available screening programs often result in late-stage diagnoses. Doctors use a system called TNM to classify lung cancer. This system, periodically updated by the International Association for the Study of Lung Cancer, considers factors like tumor size (T), lymph node involvement (N), and presence of distant metastasis (M) to determine the stage of the cancer. The stage is based on information gathered from a large international database of lung cancer patients (Goldstraw et al., 2016). Accurately determining the stage of lung cancer is important as both treatment options and prognosis are heavily influenced by this information.

EPIDEMIOLOGY OF NSCLC

Lung cancer ranks second in overall prevalence for both men and women, following prostate cancer in men and breast cancer in women (Bray et al., 2018). It has undergone a dramatic transformation in the past century. Once uncommon, it has become the leading cause of cancer death worldwide. This rise is strongly linked to increased smoking prevalence, particularly in developing nations.

Age

The risk of lung cancer increases steadily with age. Biological aging may contribute because over time, telomeres, the protective caps on our chromosomes, become shorter. Additionally, levels of a vital molecule called NAD+ decline. These combined effects compromise our cells' ability to mend DNA damage and eliminate abnormal cells (Campisi, 2013; Shay, 2016). While men have a slightly higher lifetime risk compared to women, there are significant racial and ethnic disparities. In the United States, lung cancer is most often diagnosed in people around 70 years old, for both men and women. Roughly half (53%) of lung cancer cases occur in people between 55 and 74 years old. The remaining cases (37%) are diagnosed in those over 75. African American men exhibit the highest age-adjusted incidence rates, with a complex pattern observed in other groups.

Smoking

Cigarette smoking is the undeniable leading cause of lung cancer, responsible for 80% of all cases. Deep sequencing studies estimate that a single year of smoking a pack of cigarettes daily can inflict an average of 150 mutations on normal lung cells, highlighting the significant damage caused by smoking. Numerous investigations consistently demonstrate a 10-fold or greater increase in lung cancer risk among smokers compared to non-smokers. The Among the largest relevant studies, American Cancer Society's cohort study found a more than 20-fold increase in lung cancer rates among men who were current smokers at the outset of the follow-up period in the early 1980s. In contrast, even the most severe and prolonged exposures to asbestos, a well-known occupational risk factor for lung cancer, elevate risk by a maximum of only about fivefold (Araujo et al., 2020).

Geographic Distribution

Developed countries currently experience the highest burden of lung cancer, both in terms of incidence and mortality. While lower rates are reported in developing regions, limited data collection in these areas might underestimate the true picture. Disparities also exist within developed nations. Despite a decline in lung cancer rates for both white and black men, the incidence remains significantly higher among black men (Jemal et al., 2010). Conversely, Asian Americans, Pacific Islanders, and Hispanic women exhibit the lowest rates.

THERAPEUTIC POTENTIAL OF MEDICINAL PLANTS

Traditional medicine has been practiced for generations across societies. Rooted in cultural theories, beliefs, and experiences, it is used not only to treat illness but to maintain health (Kumara et al., 2012). Traditional herbal medicine has a long history, evolving from tinctures and teas to purified compounds. Local knowledge about medicinal plants, passed down through generations in families and cultures, has yielded remarkable discoveries. These plants have provided us with essential drugs like pain relievers (morphine), cough suppressants (codeine), blood pressure medications (reserpine), heart medications (digoxin), cancer treatments (vinblastine, taxol), and anti-malarials (quinine, artemisinin). Medicinal plant research continues to be a valuable source of new leads for treating cancer, malaria, heart disease, and neurological disorders (Kumar et al., 2015).

Plants not only provide natural means of treatment but are available at affordable prices (Ghosh et al., 2008). They are a rich source of novel bioactive compounds. Plants have evolved and adapted over millions of years to withstand bacteria, insects, fungi and weather to produce unique, structurally diverse secondary metabolites. Thus, they exhibit diverse structures and valuable ethnopharmacological properties that provide a primary source of medicines for early drug discovery (McRae et al., 2007)

Natural products and their synthetic derivatives have been developed and used in clinical medicine, with successful treatments across a wide range of diseases. The 19th century witnessed a surge in plant-derived drug discoveries with the isolation of numerous alkaloids, including morphine, cocaine, and quinine, from plants like poppy, coca, and cinchona. These discoveries encouraged the wider exploration of bioactive plant compounds, both natural and modified, as effective medicines. The World Health Organization estimates 80% of the world's population relies on medicinal plants for basic healthcare. Currently, approximately 25% of modern drugs are derived from plants. Natural products have a long history as medicines. Drug discovery from these sources employs botanical, chemical, and biological techniques. Recent advancements in molecular modeling promote the use of plant chemicals to treat various diseases.

USE OF MEDICINAL PLANTS IN CANCER TREATMENT

Many medicinal plants contain various bioactive compounds (phytochemicals) like alkaloids, triterpenoids, and flavonoids. These phytochemicals can be effective for lung cancer prevention and treatment. These natural products act by targeting various molecules involved in angiogenesis (blood vessel formation), metastasis (cancer spread), and reducing severe side effects from conventional therapies (Jeong et al., 2011)

Dietary Plants and their Benefits in Lung Cancer Treatment

Cruciferous vegetables, like broccoli and cauliflower, are rich in compounds called glucosinolates, which can be converted to isothiocyanates by an enzyme called myrosinase. Some isothiocyanates, like phenethyl isothiocyanate and sulforaphane, are being studied for their potential to prevent cancer. For instance, studies suggest that benzyl isothiocyanate might inhibit the growth of certain lung cancer cells that are resistant to other medications (Shapiro et al., 2001). Soybeans are another source of potentially beneficial compounds. Genistein, the most abundant isoflavone in soybeans, may enhance the effects of certain cancer therapies in lung cancer cells, without harming healthy lung cells (Shiau et al., 2010).

The Fabaceae plant family (pea family), known for its diverse range of natural chemicals, is effective in fighting NSCLC (Gan et al., 2020). These phytochemicals, including isoflavones, lectins, saponins, and phenolic compounds, possess antioxidant properties and may play a role in both preventing and treating cancer (Sharma et al., 2017). Interestingly, research has identified a group of proteins called FAM83 (including FAM83A, B, C, D, F, and H) that are more active in NSCLC patients. Higher levels of these FAM83 protein messages (mRNA) were linked to a better chance of survival for lung cancer patients (Okabe et al., 2015). Furthermore, a specific protein within this group, FAM83B, shows potential as a tool for diagnosing and predicting the course of lung squamous cell carcinoma (SCC). Studies suggest that FAM83B might be linked to better survival rates in SCC patients (Highland et al., 2022).

Green tea, one of the most popular beverages globally, is also found to be beneficial for protecting lung health. Studies suggest its protective effects against cancer might be due to a key component called epigallocatechin gallate (EGCG) (Khan et al., 2009; Jin et al., 2013). EGCG may work through various mechanisms, including inhibiting cell division, inducing cell death (apoptosis), and regulating signaling pathways within cells. It might also influence enzymes that metabolize carcinogens and suppress the activation of factors that promote cancer growth. Research suggests that EGCG at specific concentrations (1–40 μM) can inhibit the independent growth of lung cancer cells by regulating a protein called p53, which plays a crucial role in suppressing tumor development (Khan et al., 2009; Jin et al., 2013). Many other dietary components rich in anti-inflammatory and antioxidant properties can help protect lung function. These include fruits like bananas and apples, vegetables like tomatoes, fish, herbal tea, and even moderate amounts of marine foods (Baines et al., 2015).

Chinese Medicinal Plants in Lung Cancer Management

*Astragalus membranaceus (*AM), also known as Hwang gi, has a long history of use for various purposes. It is believed to boost vitality, improve skin health, promote urination, and aid tissue regeneration (Auyeung et al., 2016). AM extracts and their active compounds, including polysaccharides, flavonoids, and saponins (Denzler et al., 2016; Ma et al., 2017) show anti-cancer properties on human non-small cell lung cancer (NSCLC) cells. Among the extracts, ethyl acetate fraction of *Astragalus membranaceus* (EAM) showed the strongest effect. EAM treatment reduced cancer cell growth (proliferation) and triggered cell death (apoptosis) in a time- and dose-dependent manner. Further analysis revealed that EAM activates proteins involved in the cell death pathway (caspases) and alters the activity of another protein group (MAPK) crucial for cell growth (Park & Park, 2018)

Hedyotis diffusa, another Chinese medicinal herb, can inhibit cancer cell growth, induce cell death (apoptosis), and prevent the spread of cancer cells by affecting molecules like NF-κB and STAT3 (Huang et al., 2024). Combining *H. diffusa* with other herbs like *Scutellaria barbata* appears to have even stronger anti-tumor effects, potentially overcoming tumor resistance by interfering with different signaling pathways in cancer cells. *H. diffusa*, when combined with Andrographis Herba, can inhibit cell division at an early stage, blocking lung cancer cell proliferation (Liu et al., 2021). Additionally, polysaccharides isolated from Hedyotis diffusa have been shown to suppress the spread of lung cancer cells by regulating specific molecules involved in this process (Lin et al., 2019).

Adenophora (Radix adenophorae), also known as "nan sha shen" in Chinese medicine and American silver root, is an herb traditionally used to nourish the yin energy in the body. It is commonly used for lung ailments, including clearing phlegm, reducing lung inflammation, and relieving coughs. According to Traditional Chinese Medicine (TCM) principles, Adenophora has a sweet and slightly bitter taste with a cooling effect. In TCM, it is a popular choice for treating coughs, bronchitis, and lung infections, and is often included in herbal cough remedies for children (Sahashi, 2005; Liu, 2009). Adenophora is generally considered safe for consumption when used appropriately and has received a class 1 rating from the American Herbal Products Association, indicating its safety profile.

Licorice root (Radix glycyrrhizae), known as "gancao" in Mandarin, is a common ingredient in TCM. It's often used in combination with other herbs to address lung and spleen issues, relieving coughs and shortness of breath (Wang et al., 2013). Licorice root is also known to help counteract the effects of certain foods, herbs, medications, and even chemical poisoning (Fiore et al., 2005). Research suggests it can ease lung inflammation and promote mucus secretion, potentially aiding in cough relief (Aly et al., 2005). Interestingly, a specific substance extracted from licorice root, licochalcone

A, was found to be effective in fighting lung cancer cells (Asl & Hosseinzadeh, 2008).

Yang Zheng Xiao Ji (YZXJ) is a TCM formula combining 14 herbs to fight cancer. This herbal blend includes ingredients like Astragalus root, Ligustrum fruit, Ginseng root, Reishi mushroom, and Hedyotis diffusa. YZXJ is used not only to combat tumors but also to improve appetite and strengthen the immune system. Studies suggest that YZXJ may work by preventing the spread of cancer cells by inhibiting their ability to stick together and move around (Jiang et al., 2012). YZXJ has also been found to be effective in reducing angiogenesis, the formation of new blood vessels that feed tumors. Combining YZXJ with chemotherapy may improve survival rates and reduce side effects for cancer patients (Jiang et al., 2015).

Herbal Plants Under Current Studies Showing Potential Against NSCLC

Developed societies are experiencing a resurgence of interest in herbal remedies. This shift is likely driven by a growing appreciation for natural products and their potential health benefits. As a consequence, the research on herbal products within healthcare is steadily expanding. An extract from a plant called *Lysimachia capillipes* (LC-C) has been studied for their ability to fight lung cancer more effectively. This study examined how LC-C affects lung cancer cells that have become resistant to radiation therapy. The results suggest that LC-C works by targeting a protein (ERRFI1) that helps cancer cells repair radiation damage and divide. Additionally, LC-C appears to block a pathway that allows cancer cells to survive. While more research is needed, LC-C's ability to make radiation more effective warrants further investigation as a potential treatment for lung cancer patients whose cancer cells resist radiation (Wu et al. 2021).

Extracts from *Brucea javanica* also show evidence in combating non-small cell lung cancer (NSCLC) through various mechanisms. These extracts target specific mutations in NSCLC cells, potentially reducing drug resistance often seen in cancer treatment (Kim et al., 2016; 2021). Additionally, *Brucea javanica* has been shown to induce apoptosis (programmed cell death) in NSCLC cells through multiple pathways, including the JNK pathway and by triggering mitochondrial dysfunction (Wang et al., 2016; Tan et al., 2019). These extracts can also suppress the growth of cancer stem cells, which are thought to contribute to tumor regrowth (Kim et al., 2021).

The *Celastraceae* plant family has emerged as a promising area of research for treating non-small cell lung cancer (NSCLC). Compounds like celastrol, isolated from these plants, exhibit strong anti-cancer properties (Zhao et al., 2022). Celastrol works by targeting multiple processes involved in NSCLC growth and spread (metastasis). It can inhibit cancer cell invasion and induce cell death (apoptosis) (Lee et al., 2011; Hernandes et al., 2017). Interestingly, celastrol has also been shown to increase the effectiveness of radiation therapy in lung cancer cells, suggesting its potential as a radiosensitizer for NSCLC treatment. Studying the chemical components of *Celastraceae* plants has provided valuable insights into their anti-cancer mechanisms. This research could be helpful for developing new therapies to combat complex cancers like head and neck squamous cell carcinoma (Fan et al., 2014).

Jin Fu Kang (JFK), an herbal liquid, often prescribed to fight non-small cell lung cancer (NSCLC) by targeting a specific process known as lymphangiogenesis. This process involves the formation of new lymphatic vessels, which can help cancer spread. JFK appears to work by inhibiting the development and movement of lymphatic cells, potentially limiting NSCLC progression (He et al., 2016). Another herbal formula, Fuzheng Kang'ai decoction (FZKA), has been investigated for its ability to induce cancer cell death (ferroptosis) in NSCLC. FZKA might achieve this by affecting specific molecules (GPX4 and system xc-) within cancer cells (Wang et al., 2018). It suggests a new approach for treating NSCLC. Additionally, FZKA has been shown to suppress lung cancer cell growth by regulating a different molecule (miR-21-5p/PTEN) which shows its potential for controlling human lung cancer cell development. Similarly, another plant *Solanum incanum* contains an alkaloid called solamargine. Solamargine has potential benefits against four types of lung cancer. It might work by enhancing the effectiveness of TNF-alpha and TNF-beta, molecules that can kill cancer cells. Solamargine may also trigger other cell death processes in lung cancer cells. Research is also exploring the potential of triterpenoidal compounds, found in plants like ivy (*Hedera* spp.) and saikosaponins from *Bupleurum falcatum* for their anticancer properties, although their specific benefits for lung cancer require further investigation (Zhou et al., 2008).

CONCLUSION AND FUTURE PROSPECTS

Despite advancements in early cancer detection and chemotherapy, cancer remains a leading cause of death worldwide. Therefore, new approaches to prevent and treat cancer are urgently needed. Conventional cancer treatments using chemical drugs can be harsh, causing side effects in healthy tissues. For this reason, natural anticancer agents derived from plants are gaining interest. Plant-based compounds offer several advantages: they can be effective against various cancers, have fewer side effects, and target cancer cells through multiple mechanisms. Traditional herbal medicines have gained traction as a complementary treatment for lung cancer. They can increase the effectiveness of conventional treatments, improve patient survival, reduce chemotherapy side effects, and enhance quality of life. Recent advances in nanotechnology are also offering new approaches to cancer treatment. Researchers are exploring the use of nanoparticles to deliver plant-based anticancer compounds directly to tumors. This approach has the potential to improve drug delivery, reduce side effects, and target specific tissues. However, despite the growing popularity of herbal medicine, some challenges persist. These challenges involve ensuring the safety, effectiveness, and quality of herbal products. The herbal extracts used often lack standardization, and most studies have been conducted in mice, not humans. Specifically, accurately identifying the plant materials used and their active ingredients, along with standardizing production processes, are crucial for wider acceptance of herbal medicine alongside conventional treatments.

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