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The potential of natural herbal plants in the treatment and prevention of non-small cell lung cancer: An encounter between ferroptosis and mitophagy

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Highlights

- The efficacy of traditional Chinese medicine is objective and the safety is high.
- Ferroptosis and mitophagy crosstalk.
- Traditional Chinese medicine targets ferroptosis and mitophagy in the treatment of NSCLC.

Abstract

Ethnopharmacological relevance

Chinese herbal medicine constitutes a substantial cultural and scientific resource for the Chinese nation, attracting considerable scholarly interest due to its intrinsic characteristics of “multi-component, multi-target, and multi-pathway” interactions. Simultaneously, it aligns accurately with the intricate and continuously evolving progression of non-small cell lung cancer (NSCLC). Furthermore, contemporary pharmacological studies indicate that natural herbaceous plants and their bioactive compounds exhibit a diverse array of biological activities, including antioxidant, anti-inflammatory, and anti-tumor effects, among others. Additionally, these substances have been demonstrated to possess a degree of safety, particularly in terms of exhibiting comparatively lower levels of toxicity to the liver and kidneys when contrasted with conventional Western medicine. Thus, the development of herbal plants, which includes both single herbs and composite formulations, as well as their bioactive constituents, through the targeted regulation of ferroptosis and mitophagy, presents substantial potential and instills considerable hope for individuals diagnosed with NSCLC.

Aim of the review

This review aims to conduct a critical analysis of the ethnopharmacological applications of natural herbaceous plants in relation to ferroptosis and mitophagy in NSCLC. The objective is to evaluate the potential advantages of prioritizing specific phytochemical constituents found in these plants, which may serve as novel therapeutic candidates informed by ethnobotanical knowledge. Additionally, this study seeks to enhance the current pharmacological applications of natural herbaceous plants.

Methods

An investigation into natural herbal remedies for NSCLC was conducted, with a particular emphasis on the ferroptosis and mitophagy pathways. This study utilized traditional medical texts and ethnomedicinal literature as primary sources. Furthermore, relevant information related to ethnobotany, phytochemistry, and pharmacology is obtained from online databases, including PubMed and the China National Knowledge Infrastructure (CNKI), among others. “Traditional Chinese medicine compound preparations”, “single herb extracts”, “active compounds”, “NSCLC”, “ferroptosis”, and “mitophagy” were used as keywords when searching the databases. Consequently, pertinent articles published in recent years were collected and analyzed.

Results

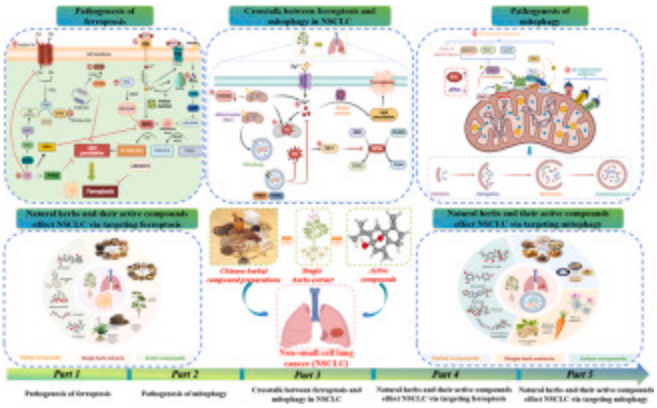
Given the complex etiology of NSCLC, treatment strategies that concentrate exclusively on ferroptosis or mitophagy often demonstrate limitations. In this regard, the utilization of herbal plants offers unique benefits in the management of NSCLC. The rationale can be summarized within the following two dimensions: Firstly, due to the molecular mechanisms of ferroptosis and mitophagy involving multiple signaling pathways (including PINK1/Parkin, HMGB1, system Xc^-/GPX4/GSH, FSP1/CoQ10/NAD (P) H, and so on), sometimes drugs with a single target are difficult to involve multiple pathways. Fortunately, there is an expanding body of evidence suggesting that various herbaceous plants and their bioactive compounds can affect multiple biological targets. Moreover, these compounds seem to interact with several targets associated with ferroptosis and mitophagy in NSCLC (such as NIX, BNIP3, FUNDC1, GPX4, FSP1, P53, Nrf2, LncRNA, and so on). Secondly, Herbaceous plants and their bioactive compounds have been shown to possess a favorable safety profile, particularly with respect to reduced hepatotoxicity and nephrotoxicity in comparison to conventional Western medicine. For example, Numerous compound formulations, such as Fangji Huangqi decoction, Mufangji decoction, Qiyu Sanlong decoction, and Fuzheng Kangai decoction, have been employed in China for millennia, and their clinical efficacy appears to be quite promising. Notably, In recent years, numerous researchers have sought to isolate active constituents from clinically effective compound formulations through the application of chemical methodologies. This endeavor has been driven by the necessity to tackle challenges related to complex ingredient compositions and sophisticated processing. These active compounds have been employed in cellular and animal studies to elucidate the molecular mechanisms underlying these formulations.

Conclusions

The Asian region has a long-standing historical tradition of employing natural herbaceous plants for traditional medicinal purposes. Phytochemical and pharmacological studies have shown that various compound preparations derived from traditional Chinese medicine, along with individual herb extracts and their active constituents, display a range of bioactive effects. These effects encompass anti-tumor, anti-inflammatory, antibacterial, and antioxidant properties, among others. Numerous traditional compound formulations originating from China have emerged as promising candidates for the development of pharmacological agents targeting NSCLC. It is noteworthy that a variety of compound formulations aimed at the ferroptosis and mitophagy pathways, which demonstrate unique therapeutic effects on NSCLC, are presently under extensive investigation by an increasing number of researchers. Therefore, it is imperative to consider *in vitro* mechanistic studies, *in vivo* pharmacological evaluations, and assessments of clinical efficacy. Furthermore, it is essential to conduct a comprehensive assessment of plant resources, implement quality

control measures, and engage in toxicological research to ensure that the data is appropriate for further examination.

Graphical abstract



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Introduction

Lung cancer is acknowledged as one of the most widespread and lethal forms of cancer globally. According to the International Agency for Research on Cancer, a branch of the World Health Organization, the global incidence of lung cancer in 2020 was documented at 11.4%, accompanied by a mortality rate of 18.0%. These statistics indicate that lung cancer is the leading cause of mortality associated with malignant neoplasms (Sung et al., 2021). Lung cancer can be categorized into two main types based on distinct organizational pathologies, including non-small cell lung cancer (NSCLC) and small cell lung cancer. Among them, NSCLC constitutes approximately 80%–85% of all lung cancer diagnoses (Wahbah et al., 2007; Chansky et al., 2017; Schabath and Cote, 2019). In clinical practice, a considerable proportion of individuals diagnosed with NSCLC do not manifest discernible symptoms in the early phases of the illness. As a result, they frequently receive a diagnosis at a later stage when seeking medical assessment (Zhu et al., 2024). Currently, patients with advanced lung cancer who are not suitable candidates for surgery primarily receive treatment modalities such as radiotherapy and chemotherapy, based on their pathophysiological mechanisms (Chen et al., 2024c). While these therapeutic modalities may offer relief from symptoms in patients, they are also linked to notable adverse reactions, which include but are not limited to bone marrow suppression, immune system suppression, alopecia, nausea, vomiting, and the potential development of drug resistance.

Moreover, the progress of radiotherapy and chemotherapy is impeded by factors like increased treatment expenses and elevated rates of disease relapse. Consequently, tackling the issues of cost reduction and efficacy enhancement in radiotherapy and chemotherapy is crucial for enhancing patients' quality of life and medical outcomes, thus constituting a significant area of focus in clinical medicine. Despite the continuous progress in the field of science and technology, which has improved the detection and management of lung cancer, the overall five-year survival rate for NSCLC remains below 20% (Ahmad et al., 2024). Consequently, there is an urgent need to explore a more comprehensive pathogenic mechanism of NSCLC and to devise safe and efficient diagnostic and therapeutic approaches. This is essential for improving the survival rates of individuals worldwide.

A considerable quantity of evidence suggests that ferroptosis and mitophagy are essential mechanisms in the regulation of tumor cell growth and proliferation across various types of cancer (Angeli et al., 2017; Yu et al., 2017; Jiang et al., 2021). The history of ferroptosis can be traced back to 2003 when erastin was first discovered to kill cancer cells. In contrast to traditional forms of cellular demise, this specific type does not exhibit the characteristic features linked with apoptosis or necrosis. Moreover, the use of particular inhibitors that target apoptosis or necrosis proves ineffective in averting this mode of cellular demise (Dolma et al., 2003). Until 2012, scholars discovered that this type of cell death induced by erastin is closely related to iron, and thus named this mode of cell death “ferroptosis” (Dixon et al., 2012). Ferroptosis is distinguished by a significant buildup of membrane lipid peroxides due to increased levels of intracellular iron. This buildup leads to the breakdown of lipid peroxides into aldehydes and reactive oxygen species (ROS). These resulting substances have the capacity to harm intracellular proteins, lipids, and nucleic acids, ultimately resulting in cellular death (Tang et al., 2021). From a morphological standpoint, the characteristics of ferroptosis primarily manifest as a decrease in cell volume, a reduction or lack of mitochondrial cristae, a rise in membrane density, and occurrences of mitochondrial fission or total loss. In contrast, the cell nucleus size remains relatively unchanged, the nuclear chromatin is not condensed, and there are no clear signs of apoptosis or necrosis (Dixon et al., 2012). In biochemistry, frropotosis is characterized by the accumulation of iron and the oxidation of lipids. A decrease in the intracellular concentration of the antioxidant glutathione (GSH) results in a significant reduction in the activity of glutathione peroxidase 4 (GPX4), consequently disrupting the balance of redox reactions. Simultaneously, the accumulation of iron ions promotes the production of significant amounts of lipids and ROS through the Fenton reaction, which ultimately leads to lipid peroxidation within the cell (Yang et al., 2014). In the field of genetics, the occurrence of ferroptosis is primarily regulated by a variety of genes and metabolic pathways, such as RPL8, IREB2, and ATP5G3 (Cao et al., 2021; Zhu et al., 2024). At present,

several research have demonstrated that ferroptosis plays an important role in the physiological and pathological processes of various diseases such as cancer, neurodegenerative diseases, blood diseases, and inflammatory diseases. Moreover, There is also empirical evidence suggesting that the induction of ferroptosis may represent a viable therapeutic strategy for the treatment of cancer (Si et al., 2022). Consequently, it is possible to hinder the progression of malignant tumors to some extent by modulating the initiation and progression of cellular ferroptosis.

Autophagy is primarily a lysosome-dependent mechanism for protein degradation that is essential for maintaining cellular homeostasis. This process encompasses the degradation and recycling of misfolded proteins and damaged organelles, thereby facilitating the preservation of the intracellular environment (Xu et al., 2024c). Autophagy can be classified into three distinct forms: macroautophagy, microautophagy, and chaperone-mediated autophagy. This classification is based on the different mechanisms through which degraded materials are transported to lysosomes. Additionally, autophagy can be further categorized as either selective or non-selective, contingent upon the specificity of the degradation targets. It is noteworthy that mitophagy represents the most extensively studied subtype of selective autophagy (Kong et al., 2024). The concept of “mitophagy” was first introduced by Lemasters in 2005, referring to the targeted removal of impaired mitochondria through lysosomal degradation. Current research suggests that mitophagy is a biological mechanism through which organisms remove mutated mitochondrial DNA. Furthermore, A reduction in mitochondrial membrane potential, in conjunction with the opening of mitochondrial permeability transition pores, is a critical prerequisite for the initiation of mitophagy (Deepak et al., 2024). Under normal circumstances, the level of mitophagy within cells is not in a state of absolute static equilibrium; abnormal or damaged mitochondria are promptly removed, while providing the necessary materials for the synthesis of new mitochondria, thereby maintaining the normal physiological functions of the cell. However, in abnormal conditions such as ischemia or malnutrition, the level of mitophagy within cells can change in response to external environmental stimuli, usually reflected in the process of disease occurrence and development. In cases where mitochondria sustain irreparable and substantial damage, or when an excessive number of mitochondria creates a burden that impedes their regular function, the cell will activate alternative pathways to eliminate the excess mitochondria, thus maintaining intracellular homeostasis (Singh, 2024). An increasing amount of evidence indicates that the efficient functioning of organizations, organs, and the entire organism is contingent upon the regulation of mitophagy. Mitochondrial autophagy is intricately associated with the pathogenesis of several clinical conditions, including neurodegenerative disorders, cardiovascular diseases, and cancer (D’Arcy, 2024). Consequently, further investigations into

mitochondrial autophagy may provide valuable insights that could inform the development of novel therapeutic strategies for NSCLC.

Indeed, an interaction exists between ferroptosis and mitochondrial autophagy, which play significant roles in regulating cellular functions and maintaining intracellular homeostasis. On one hand, mitophagy plays a crucial role in ferroptosis. Mitophagy can be a “friend” of ferroptosis, as its goal is to load damaged mitochondria into autophagosomes and degrade them through acidic hydrolases in lysosomes, thereby preventing the leakage of harmful substances within the cell. This mechanism may also regulate the concentrations of intracellular iron ions to some extent, thereby promoting the induction of ferroptosis (Yang et al., 2024b). In addition, mitophagy can also be an “enemy” of ferroptosis. Mitochondria, as a sentinel for ferroptosis, may sequester iron within the mitochondria during the early stages of mild stress or iron overload, thereby reducing the sources of ROS for ferroptosis and, to some extent, curbing the progression of ferroptosis (Granata et al., 2022). On the other hand, ferroptosis also plays a crucial role in mitochondrial autophagy. Continuous accumulation of iron has the potential to induce mitochondrial dysfunction, which may subsequently initiate the process of mitophagy. This mechanism could act as an additional source of iron, thereby contributing to lipid peroxidation. Furthermore, the activation of the mitochondrial-dependent vicious cycle can directly promote the release of iron, ROS, and lipid peroxides, thereby initiating and exacerbating the process of ferroptosis (Rademaker et al., 2022). In conclusion, the relationship between ferroptosis and mitochondrial autophagy is complex and likely involves a variety of signaling pathways and molecular mechanisms. Ongoing research is furthering our comprehension of these interactions, which not only clarifies the molecular mechanisms that govern cell death and self-regulation but may also provide substantial insights into the treatment of NSCLC.

Consequently, during our systematic review of the mechanisms that underlie ferroptosis and mitophagy, our objective is to clarify their roles in the advancement of NSCLC. This article presents a thorough analysis of how herbal plants and their bioactive compounds influence ferroptosis and mitophagy in the context of NSCLC. By doing this, it introduces new viewpoints and understandings that could guide the clinical advancement of treatments for this specific malignancy.

Section snippets

The pathogenesis of ferroptosis

Ferroptosis represents a recently identified mechanism of cell demise that relies on iron and stands apart from apoptosis, pyroptosis, and autophagy (Zhang et al., 2024a, Zhang et al., 2024b). Its hallmark features include the buildup of ferrous ions and lipid peroxides intracellularly. This phenomenon is pivotal in the development and treatment of diverse pathological conditions. Numerous studies have demonstrated that the regulatory mechanisms governing ferroptosis involve multiple signaling …

The significance of ferroptosis in NSCLC

Ferroptosis is characterized by the process of lipid peroxidation that is reliant on iron, as well as the accumulation of ROS, leading to oxidative harm to cellular components and ultimately resulting in cell demise. Recent research findings have suggested that individuals diagnosed with lung cancer show increased levels of oxygen, ROS, and lipid peroxides in their lung tissues compared to other types of tissues (Zhang et al., 2022c; Rosell et al., 2023). Additionally, studies have shown that …

The role of crosstalk between ferroptosis and mitophagy in NSCLC

The primary objective of cancer treatment is to induce apoptosis in cancerous cells, with ferroptosis—a distinct form of regulated cell death—playing a crucial role in oncological therapies. Research has demonstrated the presence of cells in NSCLC that exhibit resistance to conventional chemotherapy drugs. After incorporating ferroptosis induction into combination therapy has yielded promising results, indicating that ferroptosis may offer a viable therapeutic strategy for overcoming tumor …

Natural herbs and their active compounds block the progression of NSCLC via targeting ferroptosis

In recent years, an increasing volume of research has underscored the notion that herbal plants possess properties defined by “multiple components, multiple targets, and multiple pathways.” This multifaceted characteristic is especially pertinent to the complex and dynamic processes associated with the progression of NSCLC. Recent research in the field of contemporary pharmacology suggests that herbal remedies and their bioactive components display a wide range of biological activities. …

Natural herbs and their active compounds block the progression of NSCLC via targeting mitophagy

Mitophagy constitutes a highly conserved and multifaceted mechanism that is activatedin relation to energy metabolism and cellular self-renewal. This process is essential for theregulation of normal physiological conditions within cells and is intricately associated with the onset and progression of various pathological processes linked to diseases. In recent years, considerable advancements has been made in understanding the mechanisms by which traditional Chinese medicine formulas, extracts, …

The active compounds from herbaceous plants block the progression of NSCLC by regulating the signaling crosstalk between ferroptosis and mitophagy

Ferroptosis is a programmed cell death modality that has emerged in recent years and is closely related to NSCLC (Deng et al., 2024). Mitophagy is a type of selective autophagy, which can participate in various biological processes such as mitochondrial depolarization, hypoxia, and development, and affect the occurrence, progression, and drug resistance of NSCLC through various pathways (Yu et al., 2023). In addition, the use of modulators to target ferroptosis and mitochondria or to combine …

Conclusion and prospect

Ferroptosis and mitophagy are emerging forms of programmed cell death that have been associated with the pathogenesis of NSCLC. Pharmacological agents that enhance mitophagy, in conjunction with pharmacological inhibitors that attenuate ferroptosis, may have the potential to alleviate lung injury associated with early-stage NSCLC. As the disease advances to the mid to late stages, it inevitably places an increased burden on the organs, prompting the body to experience excessive and prolonged …

CRediT authorship contribution statement

Yujie Yang: Writing – original draft, Formal analysis. **Bing Jiang:** Writing – review & editing, Investigation, Data curation. **Lijuan Shi:** Writing – review & editing, Investigation, Formal analysis. **Lili Wang:** Writing – review & editing, Methodology, Formal analysis. **Yaru Yang:** Writing – review & editing, Methodology, Formal analysis. **Yongyu Li:** Writing – review & editing, Visualization. **Yanmei Zhang:** Writing – review & editing, Visualization. **Zhongbo Zhu:** Writing – review & editing. **Xuhui Zhang:** …

Additional notes

The plant names used in this article have been verified through http://www.worldfloraonline.org ↗. Verification date: September 9, 2024. …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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