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# Advancements in Chemoprevention of Lung Cancer and the Application of TCM

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**ABSTRACT**

Lung cancer remains the leading cause of cancer-related deaths. Despite significant advancements in surgical techniques, chemoradiotherapy, targeted therapies, and immunotherapy, the long-term survival rates for lung cancer patients remain low. Consequently, the importance of chemoprevention in lung cancer management cannot be overstated. Notably, the concept of preventive medicine in traditional Chinese medicine bears similarities to modern chemoprevention strategies and serves as a theoretical foundation for lung cancer prevention and treatment within this framework. This paper presents a comprehensive review of recent advancements in in vivo experimental research related to lung cancer chemoprevention. Furthermore, it systematically evaluates and summarizes these findings, providing a comprehensive overview of the current landscape. Additionally, we delve into the progress of clinical research in lung cancer prevention, highlighting both established results and ongoing challenges. Moreover, this paper explores the potential of traditional Chinese medicine in the field of lung cancer prevention, aiming to offer valuable insights and guidance for future investigations and practical applications. By examining these advancements and challenges, we aspire to pave the way for novel approaches and strategies in lung cancer prevention.

**Keywords:** Lung Neoplasms; Chemoprevention; Traditional Chinese Medicine; Review

## Introduction

Lung cancer has become a prominent menace to human health in recent years. Despite notable progress in personalized treatment modalities, including surgery, chemoradiotherapy, targeted therapy, and immunotherapy, it continues to be the foremost cause of cancer-related fatalities [1]. In China, the incidence of lung cancer has been consistently escalating, with 2016 statistics revealing that it has outpaced other cancers to emerge as the most widespread and lethal [2]. Although the 5-year survival rate for early-stage lung cancer can attain a high of 83%, it plummets significantly to 5%～15% for stage III patients and falls below 2% for those in stage IV. This underscores the paramount importance of timely detection, diagnosis, and intervention in enhancing patient outcomes [3]. Moreover, considering the influence of environmental factors, such as atmospheric pollution, it is urgent to adopt comprehensive prevention and control measures to curtail the ravages of lung cancer.

The concept of chemoprevention, originally introduced by Michael Sporn in 1976, relates to the use of specific chemical agents or natural substances to impede cancer development, prevent its occurrence, or delay its progression [4]. This approach represents a new avenue in cancer drug research, striving to slow down, reverse, or hinder tumor growth through pharmacological means. Its ultimate goal is to decrease tumor incidence, recurrence, and metastasis rates. Farber emphasized three main strategies for cancer prevention, collectively referred to as three-tier prevention. Primary prevention aims to eliminate or avoid carcinogens and involves the implementation of chemoprevention for healthy individuals at risk of developing cancer, also known as etiological prevention. Secondary prevention targets individuals with precancerous lesions, focusing on interrupting the carcinogenic effects of carcinogens or inhibiting their interaction with cellular DNA. Tertiary prevention centers on preventing

secondary tumors in cancer patients and utilizing chemoprevention to address recurrence and metastasis after treatment [5]. Years of clinical and experimental research have established the chemopreventive effectiveness of tamoxifen in breast cancer, retinoic acid in head and neck cancer, and aspirin in colon cancer [6-8]. Additionally, numerous chemical agents and natural botanicals, including Chinese herbal medicine, have been investigated for lung cancer chemoprevention. Although some of these substances and their extracts have demonstrated potential in preventing lung cancer, these promising results are currently limited to experimental studies, and their clinical efficacy remains unsatisfactory [5].

## Advancements in Experimental Research on Chemoprevention of Lung Cancer

Cancer chemoprevention represents a pivotal strategy in averting the development of lung cancer. Over the years, various experimental studies utilizing animal models have been conducted to identify both synthetic drugs and natural plant substances that exhibit chemopreventive properties against lung cancer. These investigations have revealed a diverse array of promising chemical agents, including retinoids, aspirin, bexarotene, 3-bromopyruvate, N-acetylcysteine, inositol, glucocorticoids (such as dexamethasone and budesonide), indomethacin, and glucose-lowering agents like pioglitazone and metformin. The effects and mechanisms, mainly involving cytokine modulation, inhibition of inflammatory carcinogenesis, suppression of cell proliferation, and promotion of apoptosis, are detailed in Table 1 [9-18]. Furthermore, numerous natural plant substances, such as green tea extract poly e, ginseng extract Rg3, curcumin, kava pepper, beetroot, β-aescin, cucurbitacin B, lycopene, Prunella vulgaris, and the traditional Chinese medicine compound antitumor B, have also demonstrated potential chemopreventive effects against lung cancer. The specific impacts and the fundamental processes behind these effects, which encompass the suppression of cellular proliferation and the enhancement of cellular apoptosis, are comprehensively outlined and detailed in Table 2 [19-28].

**Table 1.**

| Chemical compounds | Animal model | Inhibit lung tumor occurrence | Mechanism and targets |
|---|---|---|---|
| Retinoids | A/J mice | Inhibits the incidence rate of lung cancer by 50%($p<0.05$) | By affecting the expression of cytokines and chemokines IL6, IL1b, CXCL2, and CSF3, it inhibits inflammatory cancer transformation [9]. |
| Asprin | A/J mice | Inhibits the incidence rate of lung cancer by 60%($p<0.01$) | Non-selective suppression of COX expression, inhibiting inflammatory cancer transformation [10]. |
| Bexarotene | Rb1 and p53 gene knockout A/J mice | Inhibits the incidence of small cell lung cancer by 86% | Inhibit cell proliferation, promote cell apoptosis [11]. |
| 3-Bromopyruvate | A/J mice | Inhibits the incidence rate of lung cancer by 58%($p<0.01$) | Influences tumor glucose metabolism, promotes cell apoptosis through Caspase-3, PARP [12]. |
| N- acetylcysteine | NIH Swiss mice | Inhibits the incidence rate of lung cancer by 30%($p<0.05$) | Regulate the level of reactive oxygen species (ROS), eliminate oxygen free radicals [13]. |
| Myo-inositol/ Dexamethasone | A/J mice | Inositol inhibits lung cancer incidence by about 46%, dexamethasone inhibits lung cancer incidence by 41%, and the combination of the two inhibits lung cancer incidence by 71%. ($p<0.001$) | Inhibit the activation of the PI3K signaling pathway [14,15]. |
| Budesonide | A/J mice | Inhibits the incidence rate of lung cancer by 82%($p<0.05$) | Increase the expression of tumor suppressor proteins P21 and P27 by inhibiting cell growth through cyclin-dependent kinases (CDK) [16]. |
| Indomethacin | A/J mice | Inhibits the incidence rate of lung cancer by 30% | Inhibit the expression of COX-1 and COX-2 [17]. |
| Pioglitazone/Metformin | A/J mice | A dose of 850 mg/kg metformin inhibits lung cancer incidence by 58.3%, and in combination with pioglitazone, it inhibits lung cancer incidence by 53.5%($p<0.01$) | Activate peroxisome proliferator-activated receptor gamma (PPARγ), inhibit cell proliferation, and induce apoptosis [18]. |

**Table 2.**

| Natural plants and extracts | Animal model | Inhibit lung tumor occurrence | Mechanism and targets |
|---|---|---|---|
| Green tea extract (PolyE) | A/J mice | Inhibits the incidence rate of lung cancer by 59% ($p<0.05$) | Inhibit cell proliferation, promote cell apoptosis [19]. |
| Ginseng extract Rg3 | NIH Swiss mice | Inhibits the incidence rate of lung squamous cell carcinoma by 65% | By reducing JNK phosphorylation, downregulating AP-1 expression [20]. |
| Curcumin | CD-1 nude mouse | Inhibits the incidence rate of lung cancer | By inhibiting Stat3 signaling, downregulating the expression of cell proliferation markers CycD1 and $Mcm^2$ [21]. |
| Kava pepper | A/J mice | Inhibits the incidence rate of lung cancer by 50% ($p<0.05$) | Inhibit cell proliferation by affecting PCNA expression, promote caspase-3, PARP expression, and induce cell apoptosis [22]. |
| Betanin | A/J mice | Inhibits the incidence rate of lung cancer by 65% ($p<0.05$) | By affecting Caspase-3, 7, 9, and PARP expression, it promotes cell apoptosis [23]. |
| β-Sitosterol glycoside | A/J mice | Inhibits the incidence rate of lung cancer by 65% ($P < 0.0001$) | By inhibiting ALDH 1A1 and P-AKT expression, inducing the expression of tumor suppressor gene P21, and suppressing cell growth [24]. |
| Cucurbitacin B | A/J mice | Inhibits the incidence rate of lung cancer by 60% ($p<0.05$) | Inhibit cell proliferation by affecting PCNA expression, induce apoptosis [25]. |
| Lycopene | A/J mice | Inhibits the incidence rate of lung cancer by 68% ($p<0.05$) | By downregulating cyclin E to prevent cell growth from G1 to S phase, and upregulating tumor suppressor genes P21 and P27, cell growth is inhibited [26]. |
| Prunella vulgaris | nude mous, A/J mice | Reduces the incidence of lung cancer in nude mice by about 70%, significantly decreasing the number and volume of lung tumors in A/J mice. | Reduce NQO1 activity and GSH content, and inhibit tumors by suppressing the Nrf2 pathway and its downstream genes [27]. |
| Chinese herbal compound (Anti-tumor B) | NIH Swiss mice | Reduce the occurrence of lung squamous cell carcinoma by 3.1 times($p<0.05$) | Prevent cellular proliferation from transforming into squamous cell carcinoma [28]. |

## Advancements in Clinical Research on Chemoprevention of Lung Cancer

Thus far, neither early clinical studies nor phase III clinical trials have produced satisfactory results for drugs and chemicals identified through experimental research as having potential lung cancer prevention properties, such as β-carotene, aspirin, vitamin E, multivitamins, mineral supplements, selenium, budesonide, inositol, and others [29-36]. It is worth noting that β-carotene, which had exhibited antioxidant properties and the capability to hinder lung cancer occurrence in experimental settings, paradoxically elevated the relative risk of lung cancer incidence in high-risk smoking and asbestos groups during clinical trials involving caret (a combination of β-carotene and retinol) and ATBC (a combination of vitamin E and β-carotene). This escalation was accompanied by a notable surge in lung cancer-related fatalities and relative risks [37,38]. Jenny, et al. [39] conducted a phase I clinical study indicating that a plant selective for folinic acid can decrease the bronchial Ki-67 labeling index and elevate omega-3 polyunsaturated fatty acid and serum prostaglandin E3 levels, suggesting its potential to reduce tumor risk in smokers. However, further clinical validation is imperative [39]. As a result, despite numerous investigations into lung cancer chemoprevention, clinically significant breakthroughs remain elusive. The discrepancies between laboratory studies and clinical trials highlight the complexity of translating in vitro and animal model findings into effective human interventions. It is crucial to consider the multifactorial nature of lung cancer development, which includes genetic predisposition, environmental exposures, and lifestyle factors. Future research should focus on identifying biomarkers that can predict individual responses to chemopreventive agents, thereby personalizing prevention strategies. Additionally, the development of novel agents with improved efficacy and safety profiles is essential to enhance the prospects of lung cancer chemoprevention. Collaborative efforts between basic scientists, clinicians, and epidemiologists are needed to design trials that are robust and can provide clear guidance on the use of chemo preventive agents in high-risk populations.

In clinical research on lung cancer chemoprevention, it is essential to define clear research endpoints tailored to different participant populations. Previous primary chemoprevention studies have primarily focused on patients at elevated cancer risk but without a prior tumor history. Conversely, secondary chemoprevention efforts target those with both high cancer risk and precancerous lesions, such as sputum cytologic atypia or bronchial dysplasia [39]. The introduction of low-dose CT screening for high-risk groups has expanded research to include patients with ground glass opacities (GGO) on CT scans,

indicating adenocarcinoma in situ or adenomatous dysplasia [40]. Finally, tertiary chemoprevention trials concentrate on patients with a history of tobacco-induced tumors who have developed a second primary tumor [39]. The unknown endpoint presents a considerable hurdle in lung cancer chemoprevention clinical research. Initially, histological precancerous lesions are widely accepted as median study endpoints. Nevertheless, the prevalent emphasis is primarily on squamous cell precancerous lesions identified via bronchoscopic biopsy. Given the heterogeneous histological landscapes of lung cancer, determining the relevance of these precancerous lesions to all lung cancer subtypes remains challenging [41]. Moreover, chest CT scan imagery featuring atypical adenomatous hyperplasia or carcinoma in situ accompanied by ground glass opacities (GGO) is viewed as an alternative potential endpoint [40,42]. Additionally, biological markers emerge as promising endpoints in lung cancer prevention research. For example, the Ki-67 immunoassay proliferation index has been utilized, with celecoxib exhibiting a decrease in Ki-67 expression within normal bronchial epithelium in various positive lung cancer prevention investigations [43]. Furthermore, transcriptional signatures of oncogenes or tumor suppressor genes in bronchial cells, proteomics of tissue biopsies, and serum proteomics offer additional avenues as potential endpoints. Studies have revealed that the overexpressed PI3K gene in bronchial brush cells correlates with lung cancer or dysplasia, underscoring its potential as a target for inositol intervention [44].

## The Application Prospects of Traditional Chinese Medicine in the Chemoprevention of Lung Cancer

As early as in the "Suwen: Great Treatise on Four Qi and Regulating Spirit," traditional Chinese medicine emphasized proactive measures. It advocated that the wise practitioner treats imbalances before they lead to disorders, rather than waiting for the disease to manifest. Once a disease takes root, treating it becomes more challenging, similar to the proverbial difficulty of retrieving a cone fallen into a well. Traditional Chinese medicine aims to forestall the onset of disease, applying this proactive philosophy in all clinical settings. By intervening early in all stages of disease development, it champions the concepts of preemptive diagnosis and preventing the progression of existing illnesses. This approach bears similarities to the three-tiered prevention strategy employed in lung cancer care, offering a theoretical foundation for the prevention and treatment of lung cancer using traditional Chinese medicine. The integration of Traditional Chinese Medicine (TCM) into global oncology practices raises significant ethical questions that must be carefully considered. One of the primary concerns is the potential for cultural misappropriation, as TCM is deeply rooted in Chinese culture and philosophy. It is essential to ensure that the use of TCM in oncology respects the origins and principles of this ancient practice while integrating it with Western medical standards. Another ethical issue involves patient safety and the efficacy of TCM treatments. Rigorous scientific validation is required to establish the safety and effectiveness of TCM therapies for cancer patients. This includes conducting clinical trials that adhere to international standards, ensuring that patients are fully informed about the potential risks and benefits of these treatments. Furthermore, the ethical integration of TCM into oncology practices requires ongoing dialogue between practitioners of both medical systems. This dialogue should foster mutual respect and understanding, leading to collaborative approaches that enhance patient care and outcomes. By addressing these ethical implications, the global healthcare community can work towards a more inclusive and comprehensive approach to cancer treatment that honors the best of both traditional and modern medical practices.

The efficacy of traditional Chinese medicine prescriptions arises from the synergistic effects of numerous medicinal ingredients. The diversity of these chemical constituents forms the material foundation of their therapeutic benefits and poses a significant focus and challenge in the evaluation of quality. With the reform of the drug review and approval system, a quality standard system for traditional Chinese medicine preparations has been established, encompassing standards for herbs, Chinese herbal medicine decoction pieces, extracts, and finished products [45]. Furthermore, the integration of advanced and sophisticated modern analytical methods, such as characteristic spectra, comprehensive recipe identification, and determination of multi-component content, into these standards has facilitated the wider dissemination and application of traditional Chinese medicine [46]. Nevertheless, the research into quality standards for traditional Chinese medicine remains a long-term and systematic endeavor. Moving forward, it is imperative to intensify foundational research on the pharmacodynamic material basis of the complex systems of traditional Chinese medicine, the principles of formulation, the metabolic processes within the body, and the mechanisms of action. This should be done with the aim of establishing and refining quality standards that are oriented towards clinical value. For those varieties containing inherent toxic ingredients, it is essential to comprehensively evaluate the relationship between therapeutic efficacy and toxicity and to establish reasonable limit standards through risk assessment [47].

In China, extensive research has been conducted by practitioners of traditional Chinese medicine on the prevention of lung cancer. In the early 1980s, Jiang Tingliang, a researcher from the Chinese Academy of Traditional Chinese Medicine, induced lung adenoma in Kunming mice using urethane. His groundbreaking findings indicated that Liuwei Dihuang Decoction could significantly reduce the incidence of lung adenoma by 44% and mitigate the carcinogenic effects of specific chemicals [48]. Zhukejian and his colleagues from the Hunan Academy of Traditional Chinese Medicine developed the Jiedu Xuanfei formula, also known as Baofeiyin. This formula, consisting of stinky peony, Solanum nigrum, Platycodon grandiflorum, and licorice, was specifically designed to treat precancerous lung lesions [49]. Critiquing the approach of focusing solely on a single component or solvent part to explain the preventive and antitumor activities of tra-

ditional Chinese medicine, Jiaxiaobin and other experts emphasized the need for a more holistic approach. They introduced the material basis component structure theory, which takes into account various components and their proportional relationships, presenting a comprehensive three-level, multi-dimensional structure for traditional Chinese medicine. Based on this theory, they proposed innovative research ideas and methods for exploring lung cancer prevention using Prunella vulgaris [50].

## The Application Prospect of Jin Fukuang Oral Liquid in the Chemoprevention of Lung Cancer

Jinfukang oral liquid stands as the pinnacle of Professor Liu Jiaxiang's scholarly approach to enhancing health Qi. Initial clinical investigations have revealed its remarkable ability to enable patients to coexist with tumors, improve survival rates, alleviate symptoms, enhance the quality of life, and modulate immune responses [51,52]. Both in vivo and in vitro experimental studies further underscore its potency in hindering tumor cell proliferation, infiltration, and metastasis, while facilitating apoptosis. Moreover, it exhibits potential in reversing tumorigenesis by reducing the expression of drug-resistant tumor cell membrane transporters [53-55]. Recent research has also highlighted Jinfukang's capacity to suppress the growth of Lewis lung cancer sca-1+ stem cell subpopulations by downregulating the expression of drug resistance-associated proteins [56]. Additionally, it demonstrates the ability to overcome acquired resistance to gefitinib by counteracting apoptosis resistance [57,58]. Furthermore, Jinfukang significantly impedes DMH-induced colorectal cancer development in rats, inhibits intestinal gland cell proliferation, promotes cell apoptosis, and influences metabolic profile alterations [59]. These compelling findings suggest that Jinfukang oral liquid holds promise as a preventive measure against lung cancer, pending further clinical validation [60]. In summary, traditional Chinese medicine's preventive approach centers on adjusting Yin and Yang and maintaining balance, serving as a guide for disease prevention and healthcare. The implementation of the academic principle of strengthening the healthy Qi in traditional Chinese medicine has demonstrated its effectiveness in lung cancer prevention and treatment through clinical and experimental research, paving the way for broader applications in chemical prevention of lung cancer.

## Contributors

G-XR is responsible for research design. YH and C-LZ assist with data collection and statistical analysis. YH drafted the manuscript, while G-XR, YH, and C-LZ revised it. All authors have reviewed and approved the final draft.

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## Competing Interests

None declared.

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