

Bibliometric Analysis on Theoretical Origins and Modern Clinical Research Progress of Xiaoqinglong Decoction in the Treatment of Lung Cancer

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Abstract:

Xiaoqinglong Decoction (XQLD), a classic traditional Chinese medicine (TCM) formula first recorded in *Treatise on Febrile and Miscellaneous Diseases*, is documented in five original entries by Zhang Zhongjing, including Articles 40 and 41 of *Treatise on Febrile Diseases*, Articles 23 and 35 in Chapter Twelve “Pulse Manifestations, Symptoms and Treatments of Phlegm-Retention Cough and Dyspnea”, and Article 7 in Chapter Twenty-Two “Pulse Manifestations, Symptoms and Treatments of Miscellaneous Gynecological Diseases” of *Synopsis of Prescriptions of the Golden Chamber*. From the perspective of TCM, the initiation and progression of lung cancer are closely correlated with dysfunction of lung diffusion and descent as well as internal retention of phlegm-fluid. XQLD exerts the effects of warming the lung to resolve fluid retention and releasing the exterior to dispel cold, which precisely targets the core pathogenesis of lung cancer. It can relieve respiratory symptoms such as cough, dyspnea and expectoration induced by lung cancer itself or radiotherapy and chemotherapy. Current evidence indicates that combined with conventional Western medical regimens, XQLD presents distinct advantages in alleviating clinical symptoms, improving patients’ quality of life and stabilizing tumor lesions, with generally favorable safety profiles.

Keywords:

Xiaoqinglong Decoction, Lung Cancer, Theoretical Origins, Clinical Research

1. Research Background and Significance

Statistics reveal that approximately 4,824,700 new cancer cases and 2,574,200 cancer-related deaths occurred in China in 2022. Among the top five most prevalent malignancies, lung cancer ranks first with an incidence of 1,060,600 cases, topping the list in both morbidity and mortality nationwide [1]. At present, multidisciplinary comprehensive therapy remains the mainstream treatment modality for lung cancer, including precise pulmonary resection, chemotherapy, radiotherapy, targeted therapy and immunotherapy. Nevertheless, most patients are diagnosed at intermediate or advanced stages, leaving limited effective therapeutic options and resulting in an overall 5-year survival rate of less than 20% [2]. Against this backdrop, accumulating

studies have validated that Chinese herbal medicines, especially classical formulas, can remarkably alleviate toxic and side effects of Western therapies, delay drug resistance, boost systemic immune function and ameliorate patients' quality of life.

XQLD is a classic formula applied for exterior cold complicated by internal fluid retention. Its pathogenesis shows a marked consistency with the clinical picture of lung cancer. Cough ranks among the key symptoms of this XQLD pattern. Research has confirmed that about 65% of patients with lung cancer first present with cough as their main complaint [3]. Tumor irritation of the airway can trigger hyperresponsiveness and produce dry cough. In Western clinical practice, anti-airway hyperresponsiveness agents are often used to relieve tumor-related cough. However, these medications are linked to adverse reactions such as sedation and respiratory suppression, making them unsuitable for prolonged administration. When the disease progresses, patients may develop persistent cough, sputum production, or dyspnea as a consequence of airway obstruction or complicated infection. Fever, also seen in the XQLD pattern, is equivalent to the low-grade fever produced by tumor necrosis or obstructive pneumonia. The nausea and dysphagia observed in this syndrome arise from stomach counterflow due to fluid pathogen attack on the stomach. TCM makes a clear distinction between retching (sound without gastric contents) and vomiting (gastric discharge without retching sound). In TCM theory, modern medical conditions such as pleural effusion and pericardial effusion fall under the category of fluid retention. Retching is essentially an excretory response: the diaphragm and abdominal muscles contract violently in an attempt to expel gastric contents, but there are no contents in the stomach. Such a reaction is characteristic of fluid retention located below the heart. In advanced lung cancer, dysphagia, nausea, and vomiting can occur as a result of esophageal compression or spread to mediastinal lymph nodes. Thirst and dysuria recorded in the XQLD pattern have identifiable causes. Thirst is triggered by fever or chemotherapy-related adverse reactions. Dysuria results from renal impairment or tumor compression of the ureters. Lower abdominal distension and diarrhea linked to the XQLD pattern relate to ascites or intra-abdominal tumor metastasis. In most cases, diarrhea stems from chemotherapy side effects.

2. Ancient Literature Research on XQLD in Lung Cancer Therapy

Textual analysis of formula origins confirms Zhang Zhongjing's original prescription: Ephedrae Herba, Cinnamomi Ramulus, and Paeoniae Radix each weighing three liang; Glycyrrhizae Radix et Rhizoma (prepared with honey), Zingiberis Rhizoma, and Asari Radix et Rhizoma also at three liang; Schisandrae Chinensis Fructus and Pinelliae Rhizoma each measured at half a sheng. Most later scholars, including Sun Simiao, Wang Huaiyin, and Chen Wuzi, preserved this foundational structure while modifying dosage proportions. For example, the Simplified Prescriptions [4] doubled Ephedrae Herba and Paeoniae Radix quantities, increased Zingiberis Rhizoma and Schisandrae Chinensis Fructus by 50%, and targeted refractory chronic cough with excessive phlegm. These adjustments highlight a strategic enhancement of therapeutic intensity for severe fluid retention syndromes, balancing efficacy with clinical safety.

Over the centuries, XQLD's clinical applications have evolved significantly, both in scope and in precision. The formula first appeared in the Treatise on Febrile Diseases, where it was indicated for treating external cold disorders marked by lingering cold symptoms and the accumulation of fluid in the cardiac region. As evidenced in the Synopsis of Prescriptions of the Golden Chamber [5], the medicinal's scope widened

to encompass cases of excessive fluid retention and severe respiratory distress with symptoms of orthopnea. Subsequent to the Song and Ming dynasties, its clinical utility was further generalized, with the Formulas of the Peaceful Benevolent Dispensary [6] integrating it into treatments for internal injuries of the lung meridian, and the Subtle Principles of the Jade Mechanism [7] prescribing its use for conditions including lung congestion, lung atrophy, nasal obstruction, rhinorrhea, and other pulmonary pathologies. This evolutionary path vividly embodies the traditional Chinese medical principle of “identical therapies for disparate diseases”: XQLD’s applicability spans both acute and chronic presentations, as long as the underlying pathogenesis involves cold-fluid invasion of the lung. Consequently, it provides a robust foundation for modern therapeutic strategies targeting chronic obstructive pulmonary disease, asthma, allergic rhinitis, and other conditions across different pathological stages.

Regarding decoction and administration methods, the original formula mandates “decoct Ephedrae Herba first and skim off the floating foam”. Most posthumous formula monographs such as *Imperial Grace Formulary of the Taiping Era* [8] and *Treatise on the Three Categories of Pathogenic Factors* [9] simplified the preparation process by converting the formula into powder with a single dose of four qian, greatly improving clinical convenience. Modification strategies were elaborated in *Treatise on Febrile Diseases*, including removing Pinelliae Rhizoma and adding Trichosanthis Radix for thirst, and eliminating Ephedrae Herba with Armeniacae Semen added for dyspnea. Subsequent physicians such as Chen Wuze, Chen Xiuyuan and Cheng Wuji further interpreted the underlying mechanisms. Cheng Wuji explicitly stated in *Explanations of Theories on Febrile Diseases* [10]: “Ephedrae Herba induces diaphoresis and is contraindicated for patients with deficient stomach cold, hence its removal. Aconiti Radix Preparata is acrid and hot; its heat property warms visceral qi while its acidity disperses cold pathogens, making it suitable for dysphagia. The two herbs synergistically eliminate cold pathogen. For dysuria and lower abdominal distension, Ephedrae Herba is removed and Poria Cocos is supplemented.” This record reflects the emphasis of later physicians on drug safety and accessibility while maintaining therapeutic efficacy.

3. Theoretical Basis of XQLD for Lung Cancer Treatment

Modern TCM physicians generally recognize that lung cancer is characterized by vital qi deficiency and pathogenic excess, yin fluid impairment, lung malnutrition and endogenous phlegm turbidity. Vital qi deficiency constitutes the pathological basis of lung cancer initiation and the critical factor for tumor recurrence and metastasis, with lung yin deficiency persisting throughout the entire disease course. Phlegm-stasis-toxin accumulation represents the primary pathological manifestation of lung cancer. Exogenous wind-cold or improper dietary intake may further aggravate internal fluid retention, forming the complex pathogenesis of exterior cold with interior fluid retention.

Shennong’s Classic of Materia Medica records that Ephedrae Herba “treats wind-stroke, febrile headache, warm malaria, induces diaphoresis to dispel pathogenic heat, relieves cough and counterflow qi, eliminates cold-heat constraint, and dissipates masses and concretions”. Modern pharmacological studies have confirmed that ephedrine dilates bronchial tubes and improves pulmonary ventilation. The Cinnamomi Ramulus adopted in Zhang Zhongjing’s classical formulas refers to Cinnamomi Cortex, which warms yang to transform qi, facilitates fluid metabolism

and reduces pleural effusion production. The *Paeoniae Radix* in the original formula refers to *Paeoniae Radix Rubra*. *Shennong's Classic of Materia Medica* notes its efficacy in “removing blood impediment and dissipating hard masses”. *Paeoniae Radix Alba* and *Paeoniae Radix Rubra* share partial therapeutic effects, yet the former nourishes yin and consolidates nutrient qi, whereas the latter disperses pathogens and activates blood circulation. *Paeoniae Radix Rubra* excels at dissipating stasis and alleviating pain, mitigating chest and hypochondriac pain in lung cancer patients.

Schisandrae Chinensis Fructus “tonifies qi and relieves adverse cough and qi counterflow”, as documented in *Shennong's Classic of Materia Medica*. *Essentials of Materia Medica* supplements its function to “consolidate dissipated lung qi and ameliorate shortness of breath caused by disordered qi diffusion throughout the body”. Its qi-tonifying effect reinforces vital qi, enhances host disease resistance and indirectly alleviates blood stasis. Contemporary research has validated that *Schisandra chinensis* polysaccharides exert potent anti-oxidative and lipid-regulating bioactivities [11].

Zingiberis Rhizoma “relieves chest distension and adverse cough qi, warms the middle jiao to arrest bleeding and induces diaphoresis”. *Authentic Materia Medica* states that it “activates heart yang, eliminates deep-seated visceral cold, disperses cold pathogens across all meridians and treats cold-induced abdominal pain”. The middle-jiao warming and cold-dissipating property of *Zingiberis Rhizoma* resolves internal fluid retention and reduces pleural effusion formation; its capacity to invigorate spleen-stomach transportation eliminates the root source of phlegm-dampness generation. As Xu Lingtai commented: “This formula exclusively treats fluid retention. Sweat originates from fluid, and the lung governs fluid metabolism. Unresolved pathogenic sweat accumulates between the lung and stomach, forming tangible lesions unresponsive to simple diaphoresis. This formula addresses all pathological links comprehensively and deserves its reputation as a miraculous remedy.”

4. Modern Literature Research on XQLD

4.1. Domestic Research Status

Research on XQLD conducted within China exhibits greater depth and volume compared to international studies, with numerous investigations substantiating its efficacy across diverse respiratory pathologies. Yu Han's [12] study validated the clinical benefits of XQLD for bronchial asthma through integrated methodologies of meta-analysis and network pharmacology. Zhang Xiaoyang [13] delved into the regulatory mechanisms underpinning modified XQLD's modulation of immune imbalance in cough variant asthma. Furthermore, Wang Ruizhi's [14] research elucidated that XQLD alleviates allergic rhinitis via suppression of NLRP3-mediated pyroptosis, thereby delineating a precise molecular target for its therapeutic action.

In terms of formula compatibility regularity, Zhang Di [15] analyzed the compatibility rules of XQLD for dispersing cold and eliminating fluid retention, while Gong Liping [16] investigated its formula-syndrome correlation based on association rule mining. Fu Yu et al. [17] screened differentially expressed genes related to allergy and lung cancer using the Genevestigator platform, and analyzed downstream regulatory proteins of XQLD targets via the IPA database. The results demonstrated that XQLD exerts anti-tumor effects by directly binding to target proteins and

modulating the expression of downstream lung cancer-related proteins, further validating its therapeutic potential against lung cancer.

Zhang Yongqiang and colleagues [18] implemented a combined therapeutic regimen integrating XQLD and governor vessel moxibustion for the treatment of lung cancer patients diagnosed with phlegm-dampness accumulation syndrome. This integrated treatment modality led to marked alleviation of cough and pain symptoms, while concurrently downregulating inflammatory biomarkers such as C-reactive protein, procalcitonin, tumor necrosis factor- α , and interleukins. In vivo animal studies [19] demonstrated that XQLD exerts anti-tumor effects by promoting apoptosis of lung cancer cells and suppressing tumor growth, which was achieved through inhibition of excessive activation of the VEGF/VEGFR signaling pathway. Cellular experiments conducted in vitro [20] elucidated that XQLD achieved anti-cancer effects by reducing MUC5AC expression in lung cancer H292 cells. This was accomplished through the suppression of transcription factor activation, downregulation of inflammatory factors, and remodeling of the tumor inflammatory microenvironment.

4.2. Overseas Research Status

At present, overseas studies on Xiaoqinglong Decoction (XQLD) remain relatively scarce. A small number of foreign scholars have begun to explore the therapeutic potential of TCM formulas for chronic diseases and conducted preliminary basic research on XQLD, yet studies directly focusing on XQLD for lung cancer treatment are limited. Nevertheless, investigations on XQLD in respiratory disorders provide scientific evidence and research directions for its potential application in lung cancer management, which can be categorized into efficacy evaluation, mechanism exploration and modified formula application.

For efficacy assessment, Gao Zhen et al. [21] reported prominent therapeutic effects of XQLD combined with conventional therapy for acute exacerbation of chronic obstructive pulmonary disease (AECOPD), including elevated overall clinical response rate, improved pulmonary function, reduced inflammatory cytokine levels and shortened symptom remission duration, complementing existing research on comprehensive efficacy evaluation of XQLD.

Wang Ruizhi et al. [22] showed that XQLD eases allergic rhinitis by blocking the NLRP3-mediated pyroptosis pathway. This discovery gives a new scientific angle for understanding the drug's pharmacological activity. Li Jun's team [23] worked on cough variant asthma in children and evaluated how modified XQLD performs across symptom relief, lung function recovery, and immune response regulation. Their findings showed that the formula not only reduced cough symptoms but also helped restore lung function and adjust immune responses. This work deepened what researchers know about how XQLD operates in respiratory diseases. On the animal side, Ruan Yongdui et al. [24] built a lipopolysaccharide-induced acute lung injury model in mice. They found that XQLD lessens lung damage by regulating arachidonic acid metabolism while also fighting cell death and inflammation at the same time. These results offer solid experimental support for bringing modified XQLD preparations into clinical use. Ren Yuzhe and colleagues [25] focused on the systemic inflammatory response in children with cough variant asthma. Their results showed that XQLD can curb excessive inflammation by targeting the IL-6/STAT3 signaling

pathway, which further confirms the clinical potential and translational value of the modified XQLD treatment approach.

4.3. Pharmacological Research on Core Medicinal Herbs of XQLD

Modern pharmacological studies have identified abundant bioactive components in Ephedrae Herba including alkaloids, volatile oils and polysaccharides, which exert diuretic, anti-asthmatic, immunomodulatory, anti-oxidative and antiviral activities [26]. Cinnamomi Ramulus contains cinnamyl alcohol, cinnamaldehyde and cinnamic acid, exhibiting antipyretic, analgesic, bacteriostatic, antiviral, vasodilatory, anti-oxidative and diuretic properties [27]. Paeoniflorin, the primary active constituent of Paeoniae Radix, displays anti-inflammatory, immunoregulatory and anti-tumor effects [28]. Schisandrae Chinensis Fructus is rich in lignans, volatile oils, polysaccharides, organic acids, terpenoids and flavonoids. Isolated monomers of lignans and polysaccharides have been extensively investigated and validated to exert robust anti-tumor activities in recent years [29]. Zingiberis Rhizoma possesses anti-metastatic bioactivities [30]. Asari Radix et Rhizoma delivers analgesic, anti-inflammatory, neuroprotective, immunosuppressive and anti-neoplastic effects [31]. Pinelliae Rhizoma exerts anti-tumor functions via inhibiting cell proliferation, inducing tumor cell apoptosis, suppressing metastasis, remodeling the immune microenvironment and enhancing chemotherapeutic efficacy; it also regulates glycolipid metabolism and alleviates tissue fibrosis [32]. Honey-fried Glycyrrhizae Radix et Rhizoma mainly contains triterpenoid saponins, flavonoids and coumarins. Relevant studies have confirmed its anti-tumor activities through mediating tumor cell apoptosis and autophagy, as well as inhibiting tumor proliferation and metastasis [33].

Collectively, XQLD exerts comprehensive pharmacological effects including anti-tumor, antitussive, anti-asthmatic, expectorant, anti-inflammatory, anti-allergic and immunomodulatory activities.

5. Conclusions

As a canonical TCM formula, XQLD has long been widely prescribed for cough and dyspnea induced by exterior cold with interior fluid retention. In recent decades, with deeper insights into the TCM pathogenesis of lung cancer and advances in modern pharmacological research, the clinical value of XQLD in lung cancer treatment has gained increasing recognition, highlighting its multi-target therapeutic advantages.

From the perspective of etiology and pathogenesis, lung cancer originates from vital qi deficiency and pathogenic excess, with lung yin deficiency as the root cause and phlegm-stasis-toxin accumulation as the superficial manifestation. In XQLD, Ephedrae Herba and Cinnamomi Cortex dispel exterior cold and warm yang to transform fluid; Paeoniae Radix Rubra dissipates hard masses, activates blood circulation and relieves pain; Zingiberis Rhizoma, Asari Radix et Rhizoma and Pinelliae Rhizoma warm and resolve internal fluid retention; Schisandrae Chinensis Fructus tonifies vital qi, consolidates dissipated lung qi and reinforces healthy qi. The formula features rigorous herb compatibility, jointly generating the therapeutic effects of dispersing cold, resolving fluid retention, diffusing the lung and relieving dyspnea, which precisely targets the core pathogenesis of lung cancer. It effectively alleviates respiratory symptoms and serous cavity effusions induced by tumor obstruction,

inflammatory reactions and internal fluid retention, embodying the TCM treatment principle of prescribing corresponding formulas for matching syndromes.

Modern pharmacological evidence reveals that XQLD modulates the expression of downstream lung cancer-related proteins, inhibits oncogenic signaling pathways, induces tumor cell apoptosis, reduces inflammatory cytokine levels and remodels the tumor inflammatory microenvironment. Clinical investigations further confirm that XQLD significantly relieves cough and pain, and downregulates inflammatory biomarkers in lung cancer patients. In summary, XQLD exerts multi-faceted therapeutic effects including anti-tumor activity, immune regulation, symptomatic relief and tumor microenvironment remodeling through multiple bioactive components and signaling pathways, conferring unique advantages in integrated traditional Chinese and Western medicine for lung cancer management. By integrating syndrome differentiation with disease diagnosis, XQLD combines findings from modern pharmacological research with the holistic regulatory philosophy of TCM.

Nevertheless, current clinical studies on XQLD are mostly limited to small-sample observational case series, lacking systematic retrospective analyses to define its applicable patient populations, characteristic therapeutic responses and safety thresholds. Although mechanistic research has achieved preliminary progress, the complex molecular regulatory networks of XQLD remain incompletely elucidated. Future research should prioritize large-scale, multi-center clinical trials to provide robust evidence supporting the widespread application of XQLD in respiratory diseases and lung cancer therapy.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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