

# Research Progress of Maidong Decoction in the Treatment of Non-small Cell Lung Cancer

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## Abstract:

Non-small cell lung cancer (NSCLC) poses a significant threat to human health and is one of the most common types of malignant tumors encountered in clinical practice. Modern medical treatments for NSCLC primarily include surgical resection, radiotherapy and chemotherapy, targeted therapy, and immunotherapy, which have demonstrated clear advantages in improving early-stage cure rates, reducing tumor burden, and prolonging survival duration. However, these approaches are also associated with numerous complications and significant toxic side effects. Traditional Chinese medicine (TCM), through its characteristic of syndrome differentiation and individualized treatment, has demonstrated advantages in alleviating postoperative adverse reactions in lung cancer patients, reducing treatment-related toxicity, and extending patient survival. Maimendong Decoction (Mai Men Dong Tang, MMD), originating from the Jingui Yaolue (Synopsis of the Golden Chamber), is a classic TCM formula that exerts its effects through multiple pathways, including replenishing qi, nourishing yin, moistening the lung, and nourishing the stomach, thereby improving the efficacy of adjuvant therapies, enhancing quality of life, and increasing survival rates. This review comprehensively analyzes the clinical applications and basic mechanisms of MMD in the treatment of NSCLC based on the available literature. Future research should further explore the anti-tumor mechanisms of MMD in adjuvant therapies, including its synergistic interactions with chemotherapy and targeted agents, optimization of dosing regimens, and standardization of safety assessments. Multi-center, large-sample randomized controlled trials are warranted to provide robust clinical evidence for the standardized application of MMD, thereby offering more comprehensive options for the clinical prevention and treatment of lung cancer.

## Keywords:

Non-small Cell Lung Cancer (NSCLC), Maimendong Decoction (Mai Men Dong Tang), Clinical Application, Antitumor Mechanisms, Adjuvant Therapy

## 1. TCM Understanding of Lung Cancer

The specific term ‘lung cancer’ does not appear explicitly in classical TCM literature. Through comparative analysis of traditional and modern medicine, lung

cancer is classified under TCM categories such as Fei Ji (lung accumulation), Xi Ben (rushing respiration), and Ke Xue (hemoptysis). The Nanjing, Chapter 56 records: 'The accumulation of the lung is called Xi Ben, located below the right hypochondrium, covering a large area like a cup ... causing aversion to cold, fever, cough, and dyspnea, and development of lung abscess.' The Yimen Buyao states: 'Superficial pathogenic factors obstruct the lung, failing to disperse ... the fetid odor is overwhelming, and even with prolonged illness it cannot be cured.' The Suwen·Yujizhen Zanglun states: 'Large bones are depleted, large muscles are sunken, the chest is full of qi, breathing is labored, and there is internal pain radiating to the shoulders and neck.' The symptoms described in these classical references bear close similarities to the main clinical manifestations of lung cancer, including blood-tinged cough and fever in the early and middle stages, and cachexia in the late stage, providing insights for later generations in studying the natural history and treatment of lung cancer.

In TCM, lung cancer is classified as a condition of root deficiency with branch excess (Ben Xu Biao Shi). The main syndrome patterns can be broadly categorized as: qi-yin deficiency, spleen-lung qi deficiency, phlegm-dampness and blood stasis obstruction, and heat-toxin congesting the lung. Among these, qi-yin deficiency syndrome is the most clinically prevalent. The treatment principles should therefore include replenishing qi and nourishing yin, tonifying the spleen and lung, and eliminating toxins and dissolving accumulation. Syndrome differentiation and treatment in TCM incorporates the therapeutic principles of protecting healthy qi, preserving stomach qi, regulating emotions, and supporting vital energy while eliminating pathogenic factors.

## 2. Composition and Pharmacological Interpretation of Maimendong Decoction

The original formula of Maimendong Decoction originates from the Jingui Yaolue: 'When fire causes counterflow of qi with uncomfortable throat, to arrest counterflow and descend qi, Maimendong Decoction governs.' The formula is composed of six medicinals: Maimendong (*Ophiopogon japonicus*), Banxia (*Pinellia ternata*), Renshen (*Panax ginseng*), Jingmi (polished rice), Dazao (*Ziziphus jujuba*), and Gancao (*Glycyrrhiza uralensis*), collectively producing the effects of replenishing qi, nourishing yin, moistening the lung, and harmonizing the stomach. In this formula, the ratio of Maimendong to Banxia is 7:1, emphasizing the heavy use of Maimendong to nourish yin, moisten the lung, generate fluids, and relieve dryness.

Pharmacological research has revealed that *Ophiopogon japonicus* saponin B (OP-B), one of the major bioactive components of Maimendong, can activate the protease and mitochondrial apoptosis pathways, inducing programmed cell death in NSCLC cell lines H460 and H1975 in a dose-dependent manner [7]. Furthermore, OP-B can directly target miRNA binding sites, upregulating the expression of miR-34a in A549 NSCLC cells, thereby inhibiting the expression of the downstream MET oncogene and exerting antitumor effects [8]. Ginsenoside Rg3, identified as the key antitumor component of Renshen, can induce programmed cellular apoptosis, inhibit epithelial-mesenchymal transition (EMT), and enhance the sensitivity of tumor cells to chemotherapeutic agents [9]. Additionally, ginseng polysaccharides and *Ophiopogon japonicus* polysaccharides have been shown to enhance the patient's antitumor immune capacity while providing protective effects on the hematopoietic system,

reducing chemotherapy-related bone marrow suppression and other adverse effects [10].

### **3. Clinical Applications of Maimendong Decoction in NSCLC**

#### **3.1. Single-Formula Treatment**

The majority of elderly and frail late-stage NSCLC patients who cannot tolerate surgery or intensive modern treatments are managed with symptomatic therapies including analgesia, hemostasis, antitussives, and gastrointestinal regulation. Zhang et al. conducted a randomized controlled study of 60 late-stage lung cancer patients with qi-yin dual deficiency, comparing a treatment group receiving Maimendong Decoction (n=30) with a control group receiving ambroxol hydrochloride oral solution (n=30). The results demonstrated that the overall effective rate for cough relief in the treatment group was significantly higher than in the control group, indicating that MMD has significant efficacy in treating cough in late-stage lung cancer with qi-yin deficiency, and is worthy of wider clinical application [12].

Wang et al. conducted clinical observation on late-stage NSCLC patients with qi-yin dual deficiency syndrome and found that treatment with modified Maimendong Decoction alone achieved a total effective rate of 82.14% for cough relief, indicating excellent efficacy in alleviating clinical symptoms and improving quality of life [13]. Renowned TCM practitioner Xu Hefen proposed that NSCLC treatment should follow the core principle of ‘replenishing qi and nourishing yin, supporting vital energy while eliminating pathogenic factors,’ and advocated that MMD can not only relieve lung cancer symptoms but also effectively reduce the risk of systemic multiple skin rashes following radiotherapy and chemotherapy [14].

#### **3.2. Alleviating Adverse Reactions of Surgery and Radiotherapy**

Surgery remains the primary curative modality for early and mid-stage lung cancer, involving resection of the primary lesion and dissection of metastatic lymph nodes. However, postoperative changes in pulmonary anatomical structure and direct tracheal exposure from lymph node dissection predispose patients to complications such as persistent cough, fever, and infection [15]. Clinical evidence confirms that administering modified Maimendong Decoction to postoperative lung cancer patients with qi-yin dual deficiency syndrome leads to significant improvement of these toxic side effects, suggesting that MMD is well suited to the physical constitution of post-lung cancer surgery patients [16].

For patients unable to tolerate surgical treatment, local ablation therapy, as a novel minimally invasive approach, offers the advantages of minimal trauma and fewer postoperative complications [17]. Liu et al. enrolled patients with late-stage lung adenocarcinoma with qi-yin dual deficiency syndrome and treated them with cryoablation combined with modified Maimendong Decoction. Follow-up observation demonstrated that MMD not only improved objective therapeutic efficacy but also effectively relieved cough, chest pain, chest tightness, fatigue, and xerostomia [18].

As radiotherapy techniques continue to mature, albeit with precise lesion localization, normal tissue damage remains unavoidable, and radiation pneumonitis is a common dose-limiting toxicity [19]. A randomized controlled study of 60 lung cancer patients undergoing radical radiotherapy compared a Maimendong Decoction plus radiotherapy group with a radiotherapy-alone group, demonstrating an incidence

of radiation pneumonopathy of only 16.67% in the MMD group, significantly lower than in the control group, suggesting that MMD can effectively prevent the development of radiation pneumonopathy [20].

### **3.3. Combined Chemotherapy Treatment**

Chemotherapy, as the predominant systemic treatment for lung cancer beyond surgery, relies on the cytotoxicity of chemical agents to eliminate tumor cells; however, it inevitably damages normal cells and produces systemic toxicity [21]. TCM adjuvant treatment alongside chemotherapy can not only enhance antitumor efficacy but also reduce toxic side effects, providing valuable support for cancer management. Clinical research has confirmed that MMD treatment in lung cancer patients undergoing chemotherapy significantly improves physical condition scores, mental state, sleep quality, and social functioning, while effectively regulating cytokine levels and improving serum tumor-related biomarkers [22].

Sun et al., after reviewing extensive clinical data, found that modified Maimendong Decoction combined with chemotherapy can significantly reduce chemotherapy-induced adverse reactions, demonstrating synergistic antitumor and toxicity-reducing effects with significant improvement in quality of life [23]. Hu et al. revealed that combined application of modified Maimendong Decoction and chemotherapy significantly attenuates the decline of Karnofsky Performance Status (KPS) score and weight loss, while effectively reducing the incidence of chemotherapy-related toxic side effects, further confirming that integrated TCM-Western medicine therapy is a safe and effective approach for mid-to-late stage NSCLC patients [24].

### **3.4. Combined with Targeted Therapy**

With the introduction of precision oncology and the deepening understanding of cellular functions and molecular targets, targeted therapy has become one of the primary treatment modalities for NSCLC, offering more tailored treatment options by precisely targeting cancer cells and minimizing damage to normal tissue [25]. In TCM, targeted agents are categorized under 'heat-toxin' drugs that readily deplete qi and yin. Maimendong Decoction, applicable to various yin-deficiency conditions, can effectively alleviate the toxic side effects brought by targeted therapy.

Li et al. found that combined treatment with Maimendong Decoction and anlotinib improves symptoms such as cough, blood-tinged sputum, wheezing, and spontaneous or nocturnal sweating in advanced NSCLC patients, reduces adverse reactions such as fatigue and diarrhea from targeted therapy, and has a good safety profile [26]. Wang et al. demonstrated that combined treatment with Maimendong Decoction and gefitinib for elderly mid-to-late stage NSCLC patients, compared with gefitinib monotherapy, significantly reduces adverse reactions such as neurotoxicity, nausea, dermatitis, and diarrhea, and effectively improves patients' quality of life and immune function [27].

Yuan et al. randomized 80 late-stage NSCLC patients into a treatment group (n = 42) and a control group (n = 38). The results demonstrated that, compared with the anlotinib-alone group, the Maimendong Decoction plus anlotinib group had a significantly reduced frequency of adverse reactions including skin rash and hepatic function damage, while tumor stability rate and KPS score were both significantly improved ( $P < 0.05$ ), strongly confirming the positive role of MMD in mitigating the toxic side effects of targeted drug therapy [28].

## 4. Mechanisms of Action of Maimendong Decoction Against NSCLC

### 4.1. Induction of Tumor Cell Apoptosis

Apoptosis, the process of genetically programmed cellular self-destruction, is critically important for the growth and homeostasis of multicellular organisms and is mediated by two principal activation pathways: the extrinsic death receptor pathway and the intrinsic mitochondrial pathway, both of which are closely linked to tumor development [29].

The JAK/STAT signaling pathway is one of the most important pathways driving the proliferation, invasion, angiogenesis, and metastasis of lung cancer cells [30]. Sun et al. established a C57BL/6 mouse Lewis lung cancer (LLC) model and assessed the expression of JAK2/STAT3 pathway-related proteins in tumor tissue by Western blot, demonstrating that modified Maimendong Decoction combined with cisplatin can exert antitumor effects by inhibiting the JAK2/STAT3 signaling pathway. Further in vitro experiments confirmed that MMD targets a node of the STAT3 signaling pathway, inducing G0/G1 and G2/M phase cell cycle arrest in A549 cells, thereby inhibiting cell growth and promoting apoptosis [31].

Fang et al. constructed a Lewis lung cancer xenograft mouse model and demonstrated that modified Maimendong Decoction significantly reduced Bcl-2 protein expression and elevated Bax protein expression in tumor tissue compared with control groups, indicating that the formula can effectively inhibit tumor growth by regulating the Bcl-2/Bax ratio in tumor tissue. In vitro experiments further showed that MMD combined with cisplatin more potently downregulated Caspase-3 and epidermal growth factor receptor (EGFR) protein expression, thereby inducing A549 cell apoptosis and more effectively inhibiting the proliferative and invasive capacity of A549 cells [32,33].

### 4.2. Enhancement of Immune Function

Tumor development is closely related to the immune state of the host. Various immune cells, including macrophages, natural killer (NK) cells, and lymphocytes, play critically important roles in the early infiltration stage of tumors [34]. Current cancer immunotherapy aims to stimulate the host's immune system to generate passive or active immunity against malignant tumors through specific recognition of tumor antigens, regulation of cellular proliferation and differentiation, and secretion of lymphokines [35].

Wang et al. compared immune function indicators in a control group receiving conventional chemotherapy with a research group receiving modified Maimendong Decoction added to conventional chemotherapy. After treatment, CD3<sup>+</sup>, CD4<sup>+</sup>, IgG, IgA, and IgM levels were significantly elevated in both groups, with all indicators superior in the research group ( $P < 0.05$ ), confirming that MMD can effectively enhance the body's antitumor immune function [36].

Using a murine lung cancer model, Lu et al. demonstrated that gavage administration of Maimendong Decoction can prevent and treat lung cancer by regulating Th1/Th2 balance to enhance body immunity. The bioactive component Ophiopogonin D was found to regulate the Wnt signaling pathway to inhibit downstream EMT progression, and to modulate NTRK1 and ITGA4 to intervene in the PI3K-Akt signaling pathway to reverse Th1/Th2 cellular imbalance [38]. Zhang et al. established a tumor lung metastasis mouse model and found that Maimendong

Decoction increased the proportion and cytotoxic activity of NK cells in peripheral blood and at tumor metastatic sites, thereby intensifying clearance of lung cancer cells and effectively reducing the number and overall burden of metastatic tumors [39].

#### ***4.3. Regulation of RNA Expression***

Long non-coding RNA (lncRNA) plays important roles in the diagnosis, treatment, and prognosis of lung cancer, serving as both markers associated with cancer state and key contributors to the acquired capabilities of cancer cells [40,41]. Reducing the expression of specific oncogenic lncRNAs can inhibit the proliferation of various cancer cell types, providing a novel cancer treatment strategy.

Jiang et al. performed whole-genome screening by gene chip analysis in Maimendong Decoction-treated LLC xenograft model mice, identifying differentially expressed lncRNAs and mRNAs. KEGG pathway analysis of predicted targets revealed significant downregulation of the JAK/STAT signaling pathway, which is closely related to tumor cell occurrence, development, differentiation, apoptosis, and metastatic invasion [42]. Xie et al. confirmed that MMD combined with Qianjinweijing Tang suppresses lung cancer through targeting lncRNA-p21 [43]. Moreover, Jiang et al. demonstrated that MMD effectively reduces tumor growth and invasive capacity by upregulating miR-149-3p while inhibiting MYC-associated zinc finger protein (MAZ) expression and suppressing the Wnt/ $\beta$ -catenin signaling pathway, thereby inhibiting tumor development [45].

#### ***4.4. Modulation of the Tumor Microenvironment***

The tumor microenvironment (TME) refers to the local biological milieu of solid tumors, encompassing malignant cells and stromal elements (fibroblasts, immune cells, endothelial cells, etc.), cytokines, microvessels, and extracellular matrix (ECM) [46]. Continuous reciprocal interactions between tumor cells and the TME drive tumor development, metastasis, and immune tolerance to treatment. Tumor-associated macrophages (TAMs) are the most abundant immune cells in the TME and exert important effects on tumor development, invasion, metastasis, and immune suppression [47].

Zhao et al. constructed a Lewis mouse LLC xenograft model and administered different concentrations of Maimendong Decoction by gavage for three weeks. ELISA analysis confirmed that MMD significantly elevated IL-10 expression levels while reducing IL-12 expression, suggesting that MMD has the potential to regulate TAM phenotype in vivo to exert tumor-inhibitory effects. Transwell migration assays and colony formation assays further confirmed that MMD significantly inhibits cell proliferation and migration in vitro [48]. A study by Du et al. using a C57BL/6N mouse model further demonstrated that MMD can significantly reduce M2-type macrophage polarization and inflammatory infiltration, providing new therapeutic concepts for clinical cancer treatment [50].

Compared with approaches that directly target cancer cells, TME-based therapy has gradually demonstrated more pronounced clinical advantages. With deepening understanding of the central role of the TME in tumor biology, lung cancer treatment is transitioning from simply eliminating tumor cells to emphasizing the regulation of the tumor microenvironment. This therapeutic philosophy targeting the TME is consistent with the holistic concept of TCM and the principle of supporting vital

energy to eliminate pathogenic factors, providing new perspectives for tumor treatment [51].

#### **4.5. Modulation of the Wnt/ $\beta$ -catenin Signaling Pathway**

Aberrant activation of the Wnt/ $\beta$ -catenin pathway can drive lung cancer formation and progression, and can regulate EMT, proliferation, apoptosis, and invasion of lung cancer cells [44]. Research on the antitumor activity of MMD in LLC mouse models confirmed that MMD effectively reduces tumor growth and invasive capacity by inhibiting the expression of MYC-associated zinc finger protein (MAZ) and suppressing the activation of the Wnt/ $\beta$ -catenin signaling pathway, while upregulating miRNA-149-3p levels, thereby inhibiting tumor development and metastasis [45].

### **5. Conclusion and Future Perspectives**

As the leading cause of cancer-related mortality worldwide, NSCLC has long presented formidable challenges to the medical community owing to its high fatality rate and unsatisfactory treatment outcomes. Maimendong Decoction can inhibit the proliferation, invasion, and metastasis of lung cancer cells through multiple mechanisms, including induction of apoptosis, enhancement of immune function, modulation of RNA expression, and remodeling of the tumor microenvironment. Clinically, MMD alleviates the toxic side effects of surgery, radiotherapy, chemotherapy, and targeted therapy, provides adjuvant synergistic therapeutic benefits, and extends patient survival, representing a valuable complementary approach in the comprehensive management of lung cancer.

However, current research on MMD in the treatment of NSCLC still has notable limitations: most clinical studies are small-scale, single-center trials with short observation periods; quality control and standardization of the formula remain challenging; and the specific bioactive components and precise molecular mechanisms have not been fully elucidated. Future research should further explore the specific antitumor mechanisms of Maimendong Decoction in adjuvant therapies, including synergistic interactions with chemotherapy and targeted agents, optimization of dosing regimens, and standardization of safety assessments. Well-designed, multi-center, large-sample randomized controlled trials are urgently needed to provide high-quality clinical evidence for the standardized application of MMD, thereby broadening its prospects in the clinical prevention and treatment of lung cancer and facilitating new drug development based on this classic formula.

### **Conflicts of Interest**

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

### **Author Contributions**

Qiang Hui: conceptualization, investigation, writing—original draft. Li Renting: supervision, writing—review & editing, project administration. Zhao Weicheng, Zhang Qianqian, Ma Xingyan: data curation, formal analysis.

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