Lung Cancer Regulation Mechanisms and Traditional Chinese Medicine: A Survey

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Abstract

This survey paper examines the intricate regulation mechanisms and signaling pathways in lung cancer, emphasizing the potential integration of Traditional Chinese Medicine (TCM) and herbal medicine into conventional cancer therapies. Lung cancer, particularly non-small cell lung cancer (NSCLC), remains a significant global health challenge due to its high mortality rate and complex molecular pathology. The paper explores gene-environment interactions, transcription factors, microRNAs, and the tumor microenvironment as critical components influencing lung cancer progression. It highlights the dysregulation of key signaling pathways such as JAK/STAT, PI3K/Akt, NF-kB, and EGFR-ERK, which are pivotal in oncogenesis and therapeutic resistance. TCM emerges as a promising adjunctive therapy, leveraging its multi-component approach to target these pathways, potentially enhancing treatment efficacy and patient outcomes. The integration of TCM with Western medicine is facilitated by advancements in network pharmacology and computational models, offering insights into the synergistic effects of herbal compounds. However, challenges persist in the scientific validation and standardization of TCM practices, necessitating rigorous clinical trials and methodological innovations. Future research should focus on elucidating the molecular mechanisms of TCM, exploring novel therapeutic targets, and refining classification systems to enhance the precision of lung cancer therapies. By addressing these challenges, TCM can be effectively integrated into cancer treatment regimens, contributing to improved patient outcomes and advancing the field of oncology.

1 Introduction

1.1 Significance of Lung Cancer

Lung cancer is among the most prevalent and lethal cancers globally, presenting significant public health challenges. In the United States, it accounts for over 160,000 deaths annually, with non-small cell lung cancer (NSCLC) responsible for approximately 80% of these fatalities [1]. The disease's high mortality rate is underscored by a dismal 5-year survival rate of less than 5% for NSCLC patients [2]. This reality underscores the urgent need for innovative therapeutic strategies and a deeper understanding of lung cancer's underlying mechanisms to enhance patient outcomes and mitigate its public health impact.

1.2 Need for Exploring Regulation Mechanisms and Signaling Pathways

Exploring regulation mechanisms and signaling pathways in lung cancer is critical for developing effective therapies. The complexity of NSCLC necessitates a thorough investigation of these pathways to understand how molecular signaling influences cellular behavior, which is essential for constructing predictive disease models [1]. Chemoresistance poses a significant treatment barrier, with calcium dysregulation via Orai3 channels identified as a factor diminishing cisplatin efficacy [2]. Additionally, microRNA (miRNA) expression dysregulation plays a pivotal role in cancer pathogenesis, impacting

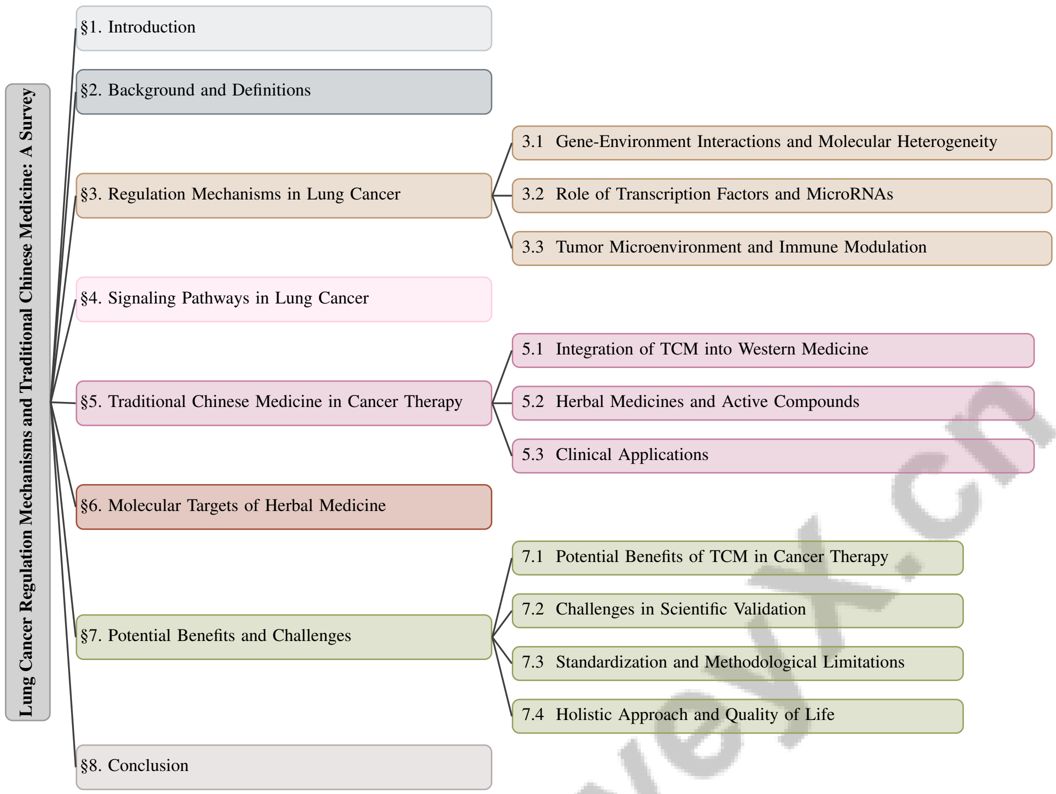

Figure 1: chapter structure

tumor initiation, progression, and metastasis [3]. The dual role of reactive oxygen species (ROS), which can both promote tumorigenesis and induce cell death, complicates the lung cancer biology landscape [4]. A comprehensive understanding of these molecular mechanisms is vital for developing targeted therapies, overcoming current treatment limitations, and improving patient outcomes.

1.3 Role of Traditional Chinese Medicine in Cancer Therapy

Traditional Chinese Medicine (TCM) has emerged as a promising adjunctive therapy in oncology, utilizing a multi-component and multi-target approach to enhance cancer treatment outcomes. The integration of TCM into cancer therapy is bolstered by advancements in network pharmacology, which elucidate the complex interactions between TCM compounds and biological networks, shedding light on its mechanisms of action. Insights into TCM's interactions with cancer-related pathways reveal its potential not only to alleviate symptoms and enhance quality of life for cancer patients but also to improve the efficacy of conventional treatments by modulating the tumor microenvironment and mitigating the adverse effects of therapies such as chemotherapy and radiotherapy [5, 6, 7, 8, 9].

TCM's potential to complement conventional therapies is further emphasized by its ability to alleviate cancer-related symptoms and reduce adverse reactions associated with standard treatments [9]. This therapeutic synergy reflects TCM's holistic approach, targeting not only the tumor but also supporting the patient's overall well-being, thus enhancing quality of life. Additionally, TCM's application in treating novel coronavirus pneumonia (NCP) highlights its broader therapeutic potential, suggesting relevance in managing complex diseases, including cancer [10].

The integration of network medicine frameworks based on the human protein interactome has deepened the understanding of TCM's mechanistic nature, revealing its effectiveness in treating symptoms and diseases through intricate biological networks [5]. The development of intelligent systems, such as large language models, further enhances the capability to analyze and interpret TCM's complex interactions, paving the way for improved diagnostic and treatment methodologies in cancer therapy [11].

As research progresses, TCM's role in cancer therapy is increasingly recognized for its potential to bridge gaps in current treatment modalities, offering a complementary approach that may enhance therapeutic efficacy and patient outcomes. Accumulating evidence supports the integration of TCM into lung cancer treatment protocols, demonstrating its efficacy in alleviating symptoms such as fatigue and pain, improving quality of life, and mitigating the side effects of conventional therapies like chemotherapy and radiotherapy, thus underscoring its significant contribution to oncology [8, 9].

1.4 Structure of the Survey

This survey is meticulously organized to provide a comprehensive exploration of lung cancer regulation mechanisms and the potential integration of Traditional Chinese Medicine (TCM) in cancer therapy. The paper begins with an **Introduction**, highlighting the significance of lung cancer, the necessity of understanding its regulation mechanisms and signaling pathways, and the possible contributions of TCM in cancer treatment. Following this, the **Background and Definitions** section offers an overview of lung cancer, its prevalence, molecular pathology, and introduces key concepts such as regulation mechanisms and signaling pathways, alongside a historical context for TCM in cancer treatment.

The survey then delves into **Regulation Mechanisms in Lung Cancer**, discussing gene-environment interactions, the role of transcription factors and microRNAs, and the influence of the tumor microenvironment. The section titled **Signaling Pathways in Lung Cancer** provides an in-depth analysis of key signaling mechanisms involved in lung cancer, specifically focusing on the JAK/STAT, PI3K/Akt, NF-kB, and EGFR-ERK pathways. It highlights the critical roles these pathways play in tumor growth, survival, and resistance to therapies while addressing the complexities and challenges associated with accurately modeling these pathways and integrating diverse data sources for comprehensive understanding and treatment strategies [12, 13].

In the section on **Traditional Chinese Medicine in Cancer Therapy**, the integration of TCM with Western medicine is explored, highlighting specific herbal medicines and their active compounds targeting lung cancer. The survey also identifies **Molecular Targets of Herbal Medicine**, discussing their mechanisms of action and integration with conventional therapies.

The **Potential Benefits and Challenges** section analyzes the advantages of incorporating TCM into cancer therapy, alongside challenges in scientific validation and standardization. Finally, the **Conclusion** summarizes the key findings, challenges, and innovations in TCM research, outlining future research directions necessary to enhance the understanding and application of TCM in lung cancer therapy.The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Overview of Lung Cancer

Lung cancer, a predominant cause of cancer-related deaths globally, exhibits complex molecular pathology and diverse histological types. The World Health Organization (WHO) classifies it primarily into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with the latter comprising about 85% of cases. NSCLC is further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, each with distinct histopathological and molecular profiles [14]. The molecular pathology involves genetic and epigenetic alterations that drive tumorigenesis and progression. A key feature in NSCLC is the overexpression of the epidermal growth factor receptor (EGFR), which enhances tumor cell motility and invasiveness [15]. Integrative analyses of prognosis datasets reveal specific gene expression patterns linked to patient outcomes, underscoring the disease's heterogeneity and the need for personalized therapeutic strategies [16]. Experimental models, such as two-dimensional NSCLC models, are vital for understanding the regulatory mechanisms and signaling pathways underlying lung cancer pathophysiology, guiding targeted therapy development and improving patient prognoses [1].

2.2 Molecular Pathology and Classification

Lung cancer classification has advanced significantly with molecular profiling and updated WHO diagnostic criteria [14]. This classification highlights the importance of molecular characteristics in defining lung cancer subtypes, enhancing diagnostic precision and treatment strategies. NSCLC subtypes, including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, exhibit distinct genetic profiles affecting treatment. Adenocarcinomas often harbor EGFR, ALK, and KRAS mutations, serving as targets for tyrosine kinase inhibitors (TKIs) and other therapies [14]. Molecular classification also emphasizes biomarkers' roles in predicting treatment responses and outcomes. For instance, EGFR mutations correlate with favorable responses to EGFR-TKIs, while KRAS mutations suggest resistance, requiring alternative treatments. PD-L1 expression levels guide immune checkpoint inhibitor use, transforming advanced lung cancer treatment [14]. Integrating molecular profiling into lung cancer classification refines diagnostic accuracy and facilitates personalized medicine approaches. Tailoring treatment to tumors' molecular characteristics optimizes therapeutic efficacy and outcomes. Ongoing research into lung cancer's molecular mechanisms is expected to advance classification systems, incorporating new biomarkers and therapeutic targets to enhance management precision. This evolution is driven by discovering driver genetic alterations and developing molecular-targeted therapies, as reflected in the revised WHO classification. Advanced computational techniques, including machine learning and multiomic data integration, will enhance tumor subtype identification and treatment strategy optimization [17, 14, 18, 19].

2.3 Key Concepts in Lung Cancer

Understanding regulatory mechanisms and signaling pathways is crucial in lung cancer research, elucidating the disease's pathophysiology and informing therapeutic development. These mechanisms involve complex interactions between genetic alterations and cellular processes driving tumorigenesis and progression. EGFR mutations significantly influence tumor dynamics, serving as diagnostic markers and therapeutic targets for TKIs [14]. Key signaling pathways, including EGFR, PI3K/Akt, and MAPK, regulate cancer cell proliferation, survival, and metastasis. Understanding these pathways' dynamics and sensitivity is vital for developing effective therapies, as they dictate cellular responses to stimuli and therapeutic agents [20]. The challenge of predicting kinase inhibitor responses in specific cancer cell lines highlights the need for robust models integrating drug-kinase interaction data with in vitro screening results [21]. Integrating multiple omics datasets is essential for identifying shared and distinct molecular markers across cancer types, enhancing diagnostic and therapeutic precision [22]. Machine learning algorithms utilizing microRNA (miRNA) expression data further improve diagnostic capabilities, offering breakthroughs in early detection and personalized treatment approaches [19]. The complexity of lung cancer's regulatory mechanisms and signaling pathways necessitates a multiscale modeling approach to capture the interplay between molecular signaling and cellular behavior. Such models are crucial for overcoming current treatment limitations, particularly in addressing drug resistance and enhancing patient outcomes [23]. Continued research into these key concepts will be vital for developing innovative therapies targeting the molecular underpinnings of lung cancer.

2.4 Traditional Chinese Medicine in Historical Context

Traditional Chinese Medicine (TCM), with a history spanning millennia, employs a holistic approach to health and disease management. Central to TCM are the principles of balancing yin and yang and the harmonious interaction of the five elements, governing the body's energy flow, or "Qi" [24]. This ancient system uses various therapeutic modalities, such as acupuncture and herbal medicine, aimed at restoring balance and promoting healing by addressing individual symptom patterns, paralleling modern precision medicine [24]. Historically, TCM has significantly contributed to cancer treatment, with strategies designed to address the disease's complexity through actions like clearing heat, eliminating dampness, and detoxification [9]. This framework is particularly relevant in oncology, where comprehensive treatment is essential for managing both the tumor and the patient's overall well-being. The integration of TCM with contemporary scientific methodologies has enhanced its application in oncology. The complexity of TCM, where each herb comprises multiple chemicals targeting various proteins, presents challenges for scientific study using modern biomedical knowledge [5]. However, advancements in network pharmacology and intelligent systems, such as the enhancement of large language models (LLMs) through prompt engineering, have facilitated a deeper understanding of TCM's multifaceted interactions and its potential in cancer therapy [11]. As TCM evolves, its historical context in cancer treatment serves as a foundation for harmonizing ancient practices with contemporary scientific methodologies. This integration enhances the understanding of TCM's therapeutic mechanisms and supports its application in alleviating cancer-related symptoms

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and mitigating conventional treatment side effects, fostering a holistic approach to patient care [8, 9, 25]. This synergy not only clarifies TCM's role in oncology but also paves the way for innovative treatment modalities that improve patient outcomes.

3 Regulation Mechanisms in Lung Cancer

Lung cancer regulation is characterized by complex biological mechanisms that drive its pathogenesis and progression. Central to this is the interplay between genetic predispositions and environmental exposures, necessitating comprehensive analyses that consider multiple genetic and environmental factors. As illustrated in Figure 2, the hierarchical structure of regulation mechanisms in lung cancer emphasizes the significance of gene-environment interactions, molecular heterogeneity, and the roles of transcription factors and microRNAs. Additionally, it highlights the tumor microenvironment's impact on immune modulation, underscoring the key components and challenges in understanding and targeting lung cancer pathogenesis and progression. Advanced methodologies, such as those employing relative error loss functions and integrative probabilistic frameworks, have enhanced the identification of significant genomic aberrations and patient subgroups, thereby improving risk prediction and therapeutic strategies [18, 26, 27]. These interactions are crucial for understanding lung cancer's variability and its complex etiology.

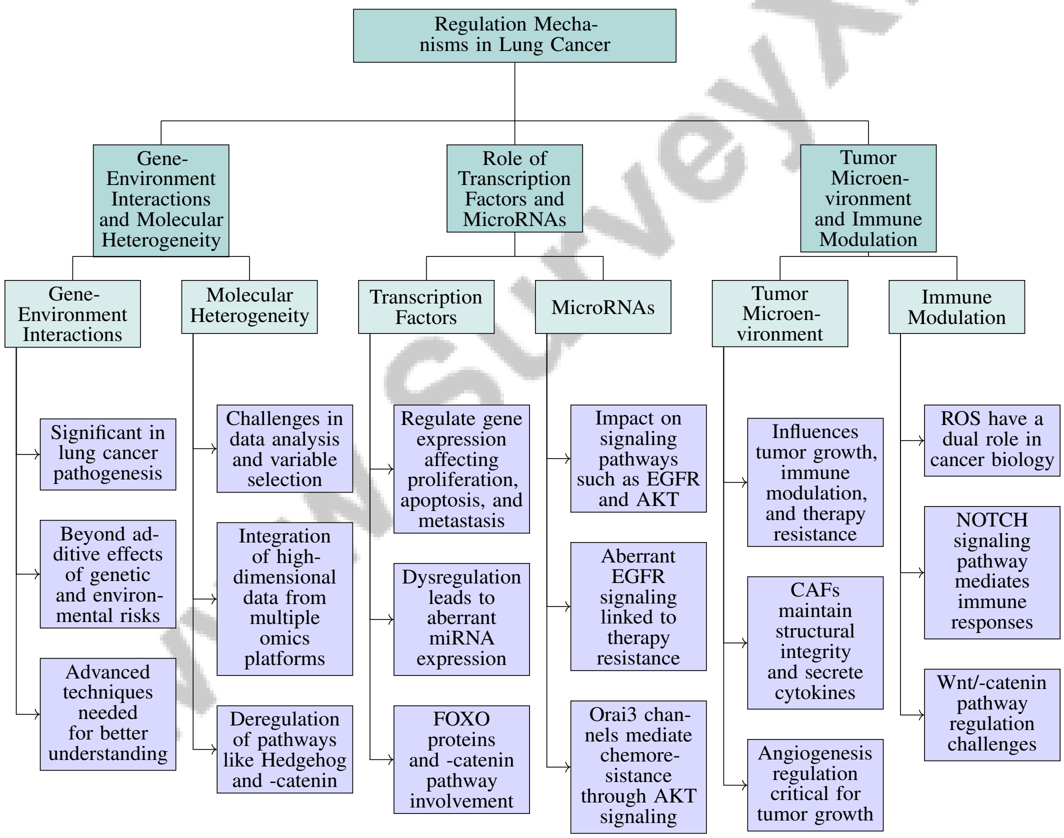

Figure 2: This figure illustrates the hierarchical structure of regulation mechanisms in lung cancer, emphasizing gene-environment interactions, molecular heterogeneity, the role of transcription factors and microRNAs, and the tumor microenvironment's impact on immune modulation. Each category highlights key components and challenges in understanding and targeting lung cancer pathogenesis and progression.

3.1 Gene-Environment Interactions and Molecular Heterogeneity

Gene-environment (G × E) interactions play a significant role in lung cancer's pathogenesis, revealing complexities beyond the additive effects of genetic and environmental risks [27]. Traditional methods often fail to capture these interactions, prompting the use of advanced techniques like relative error-based criteria to better understand their collective influence on lung cancer risk [27]. The tumor microenvironment (TME) further complicates lung cancer dynamics by influencing molecular behaviors and cellular interactions, with current models struggling to integrate G × E interactions within the TME [15]. Molecular heterogeneity across lung cancer cases poses challenges for data analysis and variable selection, necessitating the integration of high-dimensional data from multiple omics platforms to identify cancer subtypes and biomarkers [16, 18].

The deregulation of pathways such as Hedgehog (Hh) and -catenin, implicated in various cancers, underscores the need for advanced modeling techniques that accurately capture dependencies in multi-level pharmacogenomic data [28]. Methodologies like CoFu, which leverage gene community structures, enhance our understanding of lung cancer's molecular heterogeneity [22]. Challenges in distinguishing cancerous from non-cancerous samples due to high false positive and negative rates further complicate diagnostics [19]. Addressing these issues requires innovative diagnostic approaches and enhanced computational models to reliably interpret the molecular heterogeneity driven by G × E interactions and other regulatory mechanisms.

3.2 Role of Transcription Factors and MicroRNAs

Transcription factors and microRNAs (miRNAs) are crucial in regulating gene expression, impacting cellular processes such as proliferation, apoptosis, and metastasis in lung cancer. Dysregulation of transcription factors can lead to aberrant miRNA expression, contributing to cancer progression [3]. Transcription factors like FOXO proteins regulate apoptosis and cell cycle arrest, influencing tumor growth and survival [29]. The -catenin pathway exemplifies how transcriptional activity is modulated through hierarchical mechanisms, with disruptions leading to uncontrolled proliferation [30]. The interplay between transcription factors and miRNAs affects signaling pathways such as EGFR and AKT, frequently dysregulated in lung cancer. Aberrant EGFR signaling is linked to uncontrolled proliferation and therapy resistance [31], while Orai3 channels mediate chemoresistance through AKT signaling [2].

Advanced methodologies like CoFu identify commonalities in cancer datasets, providing insights into regulatory networks [22]. Despite advancements, challenges persist in modeling the complexity of cell signaling pathways, which involve numerous interactions and feedback loops [32]. Integrating domain-specific knowledge into computational models, such as BianCang's two-stage training process for TCM, may offer new insights into targeting transcriptional dysregulation in lung cancer [33]. These approaches hold promise for developing novel therapeutic strategies aimed at modulating transcription factor and miRNA activity.

3.3 Tumor Microenvironment and Immune Modulation

The tumor microenvironment (TME) is pivotal in lung cancer progression and therapeutic resistance, orchestrating interactions among cancer cells, stromal components, and immune cells. As illustrated in Figure 3, the hierarchical categorization of the TME underscores its complex impact on immune modulation, highlighting key components, pathways, and the therapeutic challenges that arise from recent studies. Cancer-associated fibroblasts (CAFs) significantly influence tumor growth, immune modulation, and therapy resistance by maintaining structural integrity and secreting cytokines and growth factors [34]. Angiogenesis regulation within the TME is critical for tumor growth and metastasis, with recent advancements leading to therapies aimed at disrupting vascular support [35]. However, TME heterogeneity poses challenges, necessitating approaches that integrate high-dimensional data from various omics platforms for a comprehensive understanding [22, 18].

Immune modulation within the TME is further complicated by reactive oxygen species (ROS), which have a dual role in cancer biology. Elevated ROS levels can promote tumorigenesis by inducing DNA damage yet also trigger apoptosis when excessive [4]. The NOTCH signaling pathway mediates immune responses within the TME, influencing tumor immunity and progression, though gaps remain in understanding its modulation [36]. The Wnt/-catenin pathway presents regulatory challenges, requiring specificity in targeting its components [30]. Inflammation within the TME enhances tumor growth and metastasis by promoting angiogenesis and suppressing anti-tumor immune responses [37]. Understanding these interactions is essential for developing therapeutic approaches that disrupt pro-tumorigenic processes.

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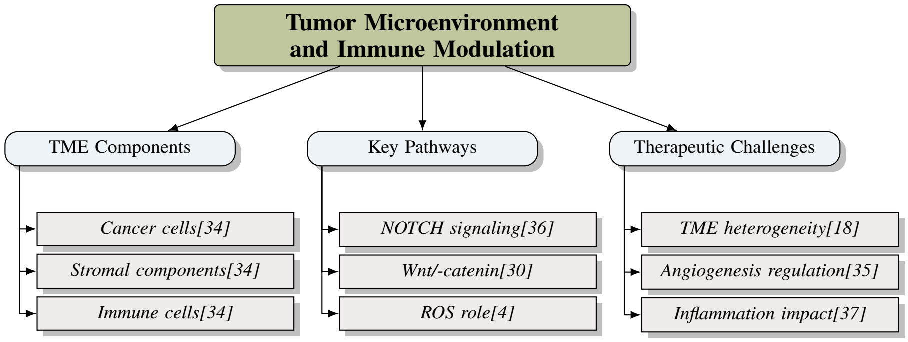

Figure 3: This figure illustrates the hierarchical categorization of the tumor microenvironment and its impact on immune modulation, highlighting key components, pathways, and therapeutic challenges based on the analysis of recent studies.

4 Signaling Pathways in Lung Cancer

4.1 JAK/STAT, PI3K/Akt, NF-kB, EGFR-ERK, and Emerging Pathways

Signaling pathways are pivotal in understanding lung cancer pathogenesis and devising targeted therapies. The JAK/STAT pathway, involving Janus kinases and signal transducers, is crucial for cytokine signaling, affecting proliferation, differentiation, and survival. Its dysregulation is linked to tumorigenesis, making it a potential therapeutic target [12, 13]. Similarly, the PI3K/Akt pathway is essential for cell growth and metabolism, with its complex network of activators and effectors underscoring its role in lung cancer [38]. The distinct functions of mTORC1 and mTORC2 within this pathway further highlight its significance [39].

The NF-kB pathway, through canonical and non-canonical mechanisms, regulates immune responses and contributes to inflammation and cancer cell survival [40]. The EGFR-ERK pathway involves the RAS-RAF-MEK-ERK cascade, promoting proliferation and survival, with modeling studies emphasizing its central role [15, 31]. Emerging pathways, such as Hedgehog signaling, influence tumor growth and metastasis through diverse mechanisms [41]. Network medicine frameworks enhance understanding of these pathways via the human protein interactome [5]. Advanced modeling techniques, including causal loop and stock-flow diagrams, provide insights into these signaling networks [32].

Exploring these pathways provides a comprehensive view of their biological roles in lung cancer. The interplay of signaling pathways in cancer-associated fibroblasts and identification of driver genetic alterations reveal numerous therapeutic targets, emphasizing ongoing research to develop innovative interventions [34, 14, 35].

4.2 Signaling Pathway Dysregulation

Signaling pathway dysregulation is a hallmark of lung cancer, driving its progression and therapy resistance. Aberrant activation of pathways like JAK/STAT, PI3K/Akt, NF-kB, and EGFR-ERK fuels oncogenic processes such as uncontrolled proliferation. For instance, JAK/STAT pathway dysregulation enhances cytokine signaling, promoting tumorigenesis, yet JAK inhibitors face challenges due to pathway complexity and patient response variability [34]. Similarly, PI3K/Akt overactivation is linked to tumor growth and therapy resistance, complicating targeting strategies [38, 39].

The NF-kB pathway, integral to inflammation and cancer cell survival, is dysregulated, enhancing tumor growth and resistance to apoptosis. Targeting NF-kB shows promise but requires personalized strategies due to treatment variability [34]. The EGFR-ERK pathway exemplifies signaling dysregulation challenges, with its interactions complicating therapeutic targeting [38]. The NOTCH pathway faces similar issues, with limited clinical trial success despite significant research [36]. The tumor microenvironment further complicates pathway interactions and contributes to therapeutic resistance, with angiogenesis regulation posing challenges due to resistance and adverse events [39].

Advanced methodologies, like Bayesian nonparametric frameworks, enhance understanding of signaling pathway dysregulation by integrating multiomic data, improving therapeutic target identification. Dysregulation presents significant challenges, emphasizing the need for comprehensive understanding to develop effective treatments that overcome resistance and improve outcomes. Recent advancements in molecular profiling and systems biology have identified key regulatory networks and therapeutic targets, such as TGF- and ERBB pathways, crucial for informing targeted therapies and enhancing clinical efficacy [14, 37, 20, 17, 35].

4.3 Challenges in Modeling and Data Integration

Modeling signaling pathways in lung cancer is challenging due to their complexity and dynamic nature. Traditional models often fail to capture intricate dependencies and interactions, especially with non-normal data distributions. The Bayesian robust chain graph model (RCGM) offers a solution by effectively modeling non-normal data while capturing dependencies among nodes [28].

A notable challenge is the dual role of signaling molecules like NF-kB, which can be both pro- and anti-tumorigenic. Studies often overlook these dual roles, leading to potential adverse effects when targeting these pathways [40]. Accurate modeling of these roles is essential for effective therapeutic strategies.

Data integration further complicates modeling, requiring synthesis of diverse datasets. The phixer algorithm exemplifies an innovative approach to reverse-engineer gene interaction networks, enhancing modeling accuracy [42]. Comprehensive data integration remains challenging due to heterogeneity and the need for robust methodologies.

Integrating differential gene expression data with other molecular datasets is crucial for accurate pathway models. A multi-faceted data augmentation approach enhances model robustness, improving predictive power across biological contexts [26]. These challenges highlight the need for advanced computational techniques and integrative frameworks to provide insights into pathway dynamics and inform therapy development.

As illustrated in Figure 4, the complexities of lung cancer modeling are multifaceted, encompassing the intricate nature of signaling pathways, the dual roles of molecules, and the integration of data through techniques like the Phixer algorithm. Furthermore, the figure underscores the importance of employing computational methods, such as Bayesian frameworks and probabilistic approaches, to navigate these challenges effectively. These approaches must manage biological data complexity and variability, identifying critical parameters and detecting tumor subtypes through probabilistic frameworks that integrate diverse genomic signatures, leading to precise therapeutic targets and improved patient stratification [20, 18].

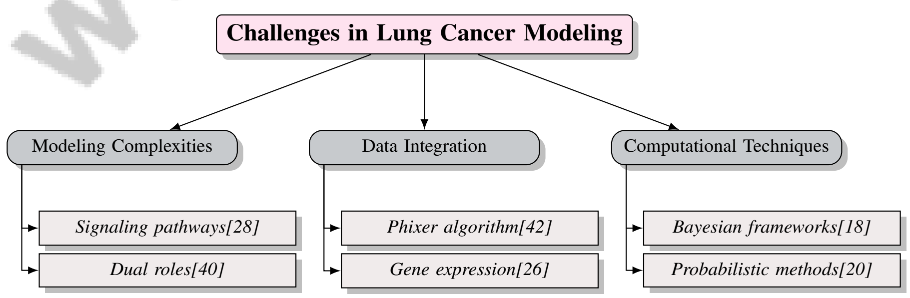

Figure 4: This figure illustrates the challenges in lung cancer modeling, focusing on the complexities of signaling pathways, the dual roles of molecules, data integration techniques like the Phixer algorithm, and the use of computational methods such as Bayesian frameworks and probabilistic approaches.

5 Traditional Chinese Medicine in Cancer Therapy

5.1 Integration of TCM into Western Medicine

Integrating Traditional Chinese Medicine (TCM) into Western medical practices offers a holistic approach that enhances conventional cancer therapies. TCM, incorporating herbal medicine, acupuncture, and dietary therapy, is recognized for improving patient outcomes by augmenting the efficacy of chemotherapy and enhancing quality of life [7]. This integration is particularly relevant in cancer care, addressing both physical and psychological aspects.

As illustrated in Figure 5, the integration of TCM into Western medical practices highlights key enhancements, data-driven methods, and applications in cancer therapy. This figure categorizes TCM's contributions, such as herbal medicine and acupuncture, alongside innovative methodologies like the BianCang model and TCM-Prompt framework, emphasizing their role in improving patient outcomes and treatment efficacy.

Significant advancements include structured training methods like BianCang, which improve syndrome differentiation and diagnostic capabilities, facilitating the effective application of TCM principles alongside Western practices [33]. Data-driven methodologies, such as a comprehensive data warehousing system, consolidate diverse TCM data sources, enhancing analysis and decision-making in TCM applications [25]. These systems enable systematic assessments of TCM's impacts on cancer therapy, promoting evidence-based integration with conventional treatments.

TCM's successful application in symptom management, as evidenced in COVID-19 treatment, underscores its potential to enhance cancer therapy efficacy [43]. Innovations in artificial intelligence, like the TCM-Prompt framework, further facilitate the integration of TCM into Western medicine by supporting complex TCM data analysis for personalized treatment plans [11].

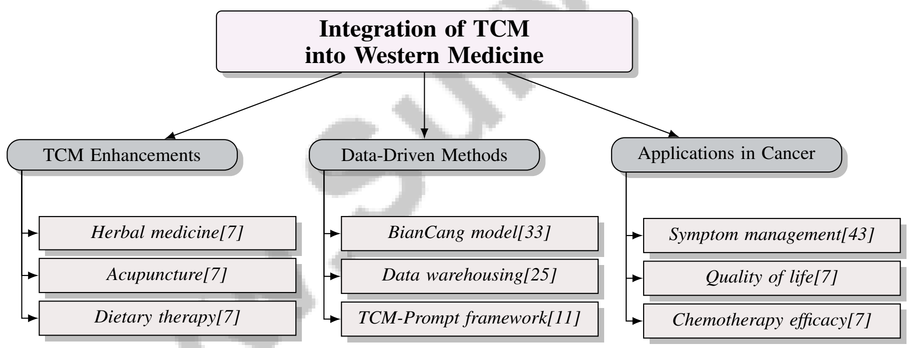

Figure 5: This figure illustrates the integration of Traditional Chinese Medicine (TCM) into Western medical practices, highlighting key enhancements, data-driven methods, and applications in cancer therapy. It categorizes TCM's contributions, such as herbal medicine and acupuncture, alongside innovative methodologies like the BianCang model and TCM-Prompt framework, emphasizing their role in improving patient outcomes and treatment efficacy.

5.2 Herbal Medicines and Active Compounds

Traditional Chinese Medicine (TCM) employs a diverse array of herbal medicines, each containing active compounds that interact with molecular pathways implicated in lung cancer. The categorization framework, THCluster, illustrates herb relationships with symptoms and diseases, aiding targeted therapeutic applications [24].

The Qingfei Paidu decoction (QFPDD), optimized for respiratory ailments, exemplifies TCM's multi-target approach, modulating cancer-related pathways to enhance therapeutic outcomes [10]. Resveratrol, a compound in TCM herbs, demonstrates integrative potential in cancer therapy due to its low toxicity and ability to target multiple oncogenic pathways, serving as a promising adjunct to conventional treatments [23]. Similarly, apigenin enhances anti-cancer efficacy in combinatorial strategies, optimizing its impact on cancer cells [44].

Advancements in computational models, such as graph neural networks, provide a quantitative framework for assessing herb compatibility and therapeutic effects [45]. Algorithms like the seq2seq model with a coverage mechanism enhance herbal formulation generation and optimization, ensuring efficacy and safety in clinical applications [46]. These innovations highlight the importance of integrating traditional practices with modern methodologies to fully harness TCM's therapeutic potential in lung cancer treatment.

5.3 Clinical Applications, Efficacy, and Future Directions

Benchmark	Size	Domain	Task Format	Metric

Table 1: Table ef presents a comprehensive overview of representative benchmarks used in evaluating the efficacy of Traditional Chinese Medicine (TCM) in cancer therapy. It includes the size, domain, task format, and the specific metrics employed to assess the performance of these benchmarks, providing a structured framework for future research validation.

Traditional Chinese Medicine (TCM) has gained attention in cancer therapy for its potential to complement conventional treatments and improve patient outcomes. TCM's holistic approach, including herbal medicine, acupuncture, and dietary interventions, is noted for alleviating adverse effects of chemotherapy and radiotherapy, enhancing cancer patients' quality of life [9]. TCM's modulation of critical signaling pathways, such as those mediated by EGFR, underscores its potential to improve therapeutic outcomes and overcome resistance to standard therapies [31].

Despite its promise, TCM's efficacy in cancer therapy requires rigorous scientific validation for integration into Western medicine. The complexity of TCM's multi-target approach poses challenges for standardization and assessment. Advanced computational models, like the Bayesian robust chain graph model (RCGM), enhance the reliability and reproducibility of TCM research by recovering dependency structures in non-normal data [28]. Table 1 provides a detailed overview of the representative benchmarks utilized in the assessment of Traditional Chinese Medicine (TCM) applications in cancer therapy, highlighting the critical parameters for scientific evaluation.

Future research should expand methodologies to develop comprehensive treatment strategies. Exploring multi-drug combinations, particularly in patient-derived primary cells, could lead to personalized treatment strategies optimizing therapeutic outcomes [21]. Integrating TCM with advanced diagnostic approaches, such as computational genomic algorithms based on microRNA expression, may enhance diagnostic accuracy in lung cancer [19].

Identifying novel biomarkers and therapeutic targets is crucial for future research. Small variations in key molecular parameters can significantly alter cellular outcomes, highlighting their potential as biomarkers for personalized medicine [1]. Targeting the Hedgehog (Hh) signaling pathway could yield new therapeutic strategies for malignancies associated with its dysregulation [41].

Sophisticated clustering methodologies have shown high accuracy in identifying cancer subtypes and relevant biomarkers, suggesting their potential for improving cancer diagnosis and treatment strategies [18]. System dynamics modeling of cell signaling pathways provides intuitive insights and facilitates quantitative analysis, serving as a valuable tool for understanding complex interactions in cancer biology and informing future therapeutic interventions [32].

As shown in Figure 6, Traditional Chinese Medicine (TCM) is increasingly recognized as a complementary approach in cancer therapy, enhancing clinical outcomes. This figure illustrates the role of TCM in cancer therapy, highlighting its clinical applications, research challenges, and future directions. It emphasizes the integration of TCM with conventional treatments to enhance patient outcomes, the need for scientific validation, and the potential for personalized treatment strategies and biomarker identification. Its integration into conventional treatments is demonstrated by its role in kinase inhibitor selectivity and cellular progression modeling. A study on A549 selectivities illustrates TCM's efficacy in differentiating cancerous from non-cancerous cells. Additionally, cellular network models provide insights into dynamic cellular phenotype progression, showing how TCM influences development stages. These examples underscore TCM's potential in refining cancer treatment strategies, enhancing therapeutic selectivity, and understanding cellular behavior, paving the way for future oncology innovations [21, 1].

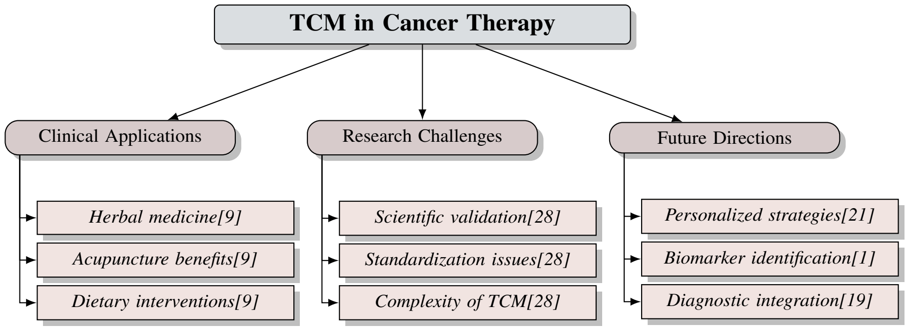

Figure 6: This figure illustrates the role of Traditional Chinese Medicine (TCM) in cancer therapy, highlighting its clinical applications, research challenges, and future directions. It emphasizes the integration of TCM with conventional treatments to enhance patient outcomes, the need for scientific validation, and the potential for personalized treatment strategies and biomarker identification.

6 Molecular Targets of Herbal Medicine

6.1 Identification of Molecular Targets and Mechanisms of Action

Method Name	Methodology Approach	Data Integration	Therapeutic Targeting
NPTCMtarget[6]	Network Pharmacology Model	Chemical And Biological	Predict Binding Targets
THCluster[24]	Path-based Random	Heterogeneous Information Network	-
MMTR[17]	Multiscale Model	Bioinformatics Data	Signaling Pathways

Table 2: Overview of methodologies for identifying molecular targets and mechanisms of action in Traditional Chinese Medicine (TCM) for lung cancer therapy. The table details the methodological approaches, data integration strategies, and therapeutic targeting capabilities of three prominent methods: NPTCMtarget, THCluster, and MMTR.

Advancing integrative oncology necessitates identifying molecular targets and elucidating mechanisms of action for Traditional Chinese Medicine (TCM) in lung cancer therapy. Table 2 presents a comparative analysis of various methodologies utilized in the identification of molecular targets and mechanisms of action in Traditional Chinese Medicine (TCM) for lung cancer treatment. The NP-TCMtarget method exemplifies a sophisticated integrative approach, predicting TCM targets by analyzing gene expression profiles linked to drug-disease interactions, thus uncovering novel therapeutic targets [6]. The THCluster framework further enriches this understanding by categorizing herbs based on their therapeutic properties, aiding in the identification of specific herbs targeting lung cancer pathways [24].

Mathematical models leveraging bioinformatics data from single-cell RNA sequencing (scRNA-seq) and proteomics simulate regulatory networks in lung cancer, particularly in response to treatments like dexamethasone (DEX) [17]. These models provide insights into TCM compounds' dynamic effects on cellular signaling pathways, elucidating their mechanisms of action. Integrating diverse data structures into a unified TCM Data Warehouse enhances clinical decision-making by synthesizing complex datasets to identify molecular targets [25].

Recent studies underscore the need for scalable models that accurately represent signaling networks' complexity in lung cancer [20]. Identifying biochemical parameters as drug targets is crucial for optimizing TCM herbal medicines' therapeutic potential. By focusing on these molecular targets, TCM can be effectively integrated into lung cancer treatments, enhancing therapeutic efficacy and improving patient outcomes.

6.2 Integration with Conventional Therapies

Integrating Traditional Chinese Medicine (TCM) with conventional cancer therapies offers a promising avenue for enhancing treatment efficacy and patient outcomes. TCM's holistic approach, including herbal medicine, acupuncture, and dietary therapy, complements conventional treatments by targeting multiple pathways and addressing both physical and psychological aspects of cancer care [9]. This synergy is particularly beneficial for managing chemotherapy and radiotherapy's adverse effects, thereby improving cancer patients' quality of life.

Utilizing network pharmacology to elucidate complex interactions between TCM compounds and biological networks is key to integrating TCM with conventional therapies. This approach provides insights into TCM's mechanisms of action, facilitating the identification of potential synergistic effects when combined with Western medical treatments [6]. Computational models like the NP-TCMtarget method further aid in predicting TCM targets and their interactions with conventional drugs, optimizing therapeutic strategies [6].

Advances in data integration methodologies, such as constructing a TCM Data Warehouse, bolster TCM's incorporation into conventional cancer treatment regimens. This system consolidates diverse data sources into a unified structure, enabling healthcare providers to make informed decisions regarding TCM integration with standard therapies [25]. By providing timely and accurate information, this data warehousing system enhances the ability to tailor treatment plans to individual patient needs, maximizing therapeutic efficacy.

Moreover, TCM's inclusion in cancer therapy has shown potential in modulating critical signaling pathways, such as those mediated by the epidermal growth factor receptor (EGFR), often implicated in resistance to conventional therapies [31]. TCM's capacity to target these pathways and enhance conventional treatments' efficacy underscores its value as a complementary approach in oncology.

7 Potential Benefits and Challenges

7.1 Potential Benefits of TCM in Cancer Therapy

Integrating Traditional Chinese Medicine (TCM) into cancer therapy offers numerous benefits that enhance conventional treatments. TCM's holistic approach, which includes herbal medicine, acupuncture, and dietary interventions, addresses cancer's multifaceted nature, supporting tumor management and patient well-being, thereby improving quality of life and treatment outcomes [47]. TCM effectively modulates critical cancer signaling pathways, such as JAK/STAT and -catenin, underscoring its therapeutic potential in oncology [13, 30]. Herbal medicines like apigenin demonstrate broad anti-cancer effects with minimal toxicity, enhancing therapeutic efficacy and counteracting resistance to standard treatments [44]. The THCluster framework aids in identifying herbal synergies, optimizing therapeutic application [24].

TCM approaches have been linked to improved immune function and reduced hospitalization durations, offering additional benefits in cancer treatment [10]. Modern AI techniques, such as graph neural networks, refine the analysis of herbal synergy, providing a robust framework for evaluating TCM's clinical efficacy [45]. Advances in EGFR-targeted therapies informed by TCM research have enhanced patient outcomes in specific cancers [31]. These developments illustrate TCM's potential to complement conventional therapies, creating a comprehensive treatment approach that integrates traditional and modern medical practices.

7.2 Challenges in Scientific Validation

The scientific validation of Traditional Chinese Medicine (TCM) faces significant challenges that hinder its acceptance in mainstream medicine. A primary issue is the insufficient scientific evidence regarding TCM's efficacy and safety, exacerbated by variability in formulations and a lack of standardized quality control measures [9]. This variability complicates consistent therapeutic outcomes and contributes to inconsistent clinical trial results due to fluctuating bioavailability of active compounds [23]. Biological interaction complexity further challenges models like NP-TCMtarget, constrained by gene signature quality and quantity, affecting predictive accuracy [6]. Cancer-associated fibroblast heterogeneity is often overlooked, leading to oversimplified conclusions [34].

Methodological limitations, including inadequate study designs, small sample sizes, and a scarcity of large-scale trials, further hinder TCM validation. The intricate nature of pathways like mTOR and JAK/STAT complicates effective targeting, and determining optimal treatment combinations remains challenging [38]. Data integration challenges persist, with unstandardized data impacting research reliability [5]. Acquiring data from TCM proprietors is difficult, necessitating standardized research methodologies [48]. Computational challenges in integrative analysis approaches reliant on complex MCMC inference require careful parameter tuning, which is resource-intensive [18]. Despite modeling advancements, capturing intricate symptom-herb interrelations remains challenging, potentially leading to suboptimal prescriptions [46].

7.3 Standardization and Methodological Limitations

Standardization of Traditional Chinese Medicine (TCM) practices is essential for integration into modern medical frameworks, yet variability in herbal formulations and therapeutic approaches presents challenges. The absence of standardized protocols for TCM compound preparation and administration contributes to inconsistencies in therapeutic outcomes, complicating efficacy and safety assessments [9]. Diverse chemical compositions of TCM herbs lead to fluctuations in bioactive compound concentrations and therapeutic effects [23]. Methodological limitations in TCM research, such as small sample sizes and lack of randomized trials, undermine findings' reliability and obstruct causal relationship establishment [23]. TCM's multi-component systems pose challenges in isolating individual compound effects and understanding synergistic interactions [24].

Advanced computational models, like network pharmacology and machine learning algorithms, offer solutions by systematically analyzing TCM compound interactions with biological networks [6]. However, model effectiveness relies on comprehensive dataset quality, often limited by noise and incompleteness [5]. Developing standardized data warehousing systems consolidates diverse TCM data sources, facilitating enhanced analysis and decision-making [25]. Such systems are crucial for TCM research reproducibility and synthesizing complex datasets into actionable insights for clinical practice.

7.4 Holistic Approach and Quality of Life

Traditional Chinese Medicine's (TCM) holistic approach is fundamental in cancer therapy, treating the whole person rather than just the tumor. This paradigm addresses cancer patients' diverse needs, including physical, emotional, and psychological well-being. TCM practices, such as acupuncture and herbal remedies, alleviate symptoms like fatigue, pain, and insomnia, improving quality of life and mitigating conventional treatment adverse effects [9, 18, 22, 7]. TCM's integrative strategy, encompassing herbal medicine, acupuncture, and dietary therapy, enhances cancer patients' quality of life by alleviating symptoms and reducing conventional treatment side effects.

TCM's strength lies in tailoring treatments to individual patient profiles, enhancing therapeutic outcomes. The approach to generating traditional Chinese prescriptions reduces herb repetition and improves recall rates, exemplifying TCM interventions' precision [46]. This personalized approach ensures treatments align with specific patient needs, maximizing efficacy. TCM's focus on restoring body balance aligns with holistic medicine principles, prioritizing disease prevention and health promotion. By addressing underlying imbalances, TCM enhances cancer patients' resilience, improving symptom alleviation and conventional treatment side effect reduction. This holistic approach improves quality of life and equips patients to cope effectively with their condition, fostering a better treatment response [8, 9, 7].

Integrating TCM into cancer care provides psychological benefits, promoting relaxation and mental well-being, crucial for patients experiencing anxiety and depression. TCM's holistic approach integrates physical and mental health strategies, such as acupuncture and herbal remedies, to alleviate symptoms like fatigue, pain, and insomnia. This comprehensive methodology enhances quality of life and serves as a valuable adjunct to conventional therapies, potentially reducing chemotherapy and radiotherapy adverse effects. By addressing the tumor microenvironment and supporting the immune response, TCM complements standard medical interventions [47, 7, 8, 9, 25].

8 Conclusion

8.1 Challenges and Innovations in TCM Research

Traditional Chinese Medicine (TCM) research in lung cancer therapy presents both significant challenges and innovative opportunities. Rigorous clinical trials are imperative to validate TCM interventions' efficacy and safety, which is essential for their integration with conventional treatments. The multifaceted nature of TCM, with its numerous active compounds and potential interactions, requires advanced methodologies to elucidate these mechanisms and their impact on lung cancer progression. Innovations in TCM research highlight the identification of novel therapeutic targets and the refinement of classification systems to enhance treatment precision. Emerging molecular targets, especially within the JAK/STAT signaling pathway, offer promising avenues for developing targeted therapies that can be aligned with TCM practices. Understanding the interactions between JAK/STAT and other signaling pathways is crucial for creating patient-specific therapeutic strategies and optimizing treatment outcomes. Furthermore, refining lung cancer classification systems is crucial for advancing personalized medicine. By exploring the relationship between genetic alterations and treatment responses, researchers can tailor TCM interventions to individual patient profiles, thereby enhancing therapeutic efficacy. This personalized approach resonates with TCM's holistic philosophy, which advocates for individualized treatment plans based on each patient's unique characteristics.

8.2 Future Research Directions

Future research on TCM in lung cancer therapy should prioritize integrating modern scientific techniques with traditional principles to improve therapeutic outcomes. A primary focus should be on elucidating the molecular mechanisms of TCM compounds, particularly their interactions with signaling pathways such as JAK/STAT and -catenin. Understanding the nuances of JAK/STAT signaling across different cancers and developing novel inhibitors for integration with other therapies is essential for enhancing patient outcomes. Additionally, creating specific inhibitors targeting -catenin's transcriptional complexes and investigating its interactions with other pathways will yield insights into more effective therapeutic strategies. Investigating calcium signaling mechanisms in lung cancer, especially the role of Orai3 channels, is another promising research avenue. Exploring pharmacological inhibitors of Orai3 channels in combination with cisplatin may lead to novel therapeutic approaches. Furthermore, enhancing the dynamics and sensitivity of signaling pathways through detailed models that incorporate substrate sequestration and feedback mechanisms will improve the predictive power of therapeutic interventions. Efforts should also focus on enhancing the theoretical framework of CoFu and its applications beyond cancer omics, broadening its relevance across various biological contexts. The integration of TCM with modern medical practices should involve exploring the interactions between TCM compounds and the gut microbiome, alongside conducting large-scale clinical trials to substantiate TCM's efficacy in treating complex diseases. In clinical research, expanding sample sizes and conducting randomized controlled trials are crucial for validating TCM's efficacy in lung cancer therapy. Additionally, developing targeted therapies that account for the heterogeneity of cancer-associated fibroblasts (CAFs) and exploring novel biomarkers through systems biology approaches will refine therapeutic strategies and enhance patient outcomes. Addressing these research directions will significantly advance the understanding and application of TCM in lung cancer therapy, ultimately contributing to the development of more effective and integrative treatment strategies.

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