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Review Article

The Application and Pathway Regulation of Traditional Chinese Medicine in Lung Cancer Treatment: An Exploratory Review

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Lung cancer is one of the cancers with the highest mortality rates. Non-small cell lung cancer (NSCLC) accounts for 85% of lung cancer cases and is often diagnosed at an advanced stage with a poor prognosis. Due to the lack of effective molecular targets, the current clinical cure rate is low, and the recurrence rate is high. Recent studies have found that active components of traditional Chinese medicine and Chinese herbal formulas can inhibit the development of NSCLC through multiple pathways and targets, effectively reducing its metastasis and recurrence rates, improving treatment side effects, and compensating for the deficiencies in drug resistance. Although treatments such as surgery, radiotherapy, targeted therapy, and immunotherapy have achieved better clinical efficacy in treating lung cancer, they still have problems such as multiple complications and severe adverse reactions. In recent years, numerous basic and clinical studies have confirmed the good effects of traditional Chinese medicine in treating lung cancer. Traditional Chinese medicine has a synergistic regulatory effect through multiple components, targets, pathways, and channels. The numerous active monomeric components and complex mechanisms of action determine that there are issues such as unclear related mechanisms of action in the prevention and treatment of lung cancer by traditional Chinese medicine. There is an urgent need to elucidate the mechanisms of action of traditional Chinese medicine in intervening in lung cancer from the perspective of modern medicine, and at the levels of molecular biology, network pharmacology, etc. This article systematically summarizes the research progress on the regulation of the above-mentioned signaling pathways and the expression of key protein molecules by traditional Chinese medicine monomers or formulas, aiming to clarify the mechanisms of action of traditional Chinese medicine in the progression of lung cancer, and to provide ideas and a theoretical basis for the in-depth study and clinical application of traditional Chinese medicine in intervening in lung cancer.

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1. Introduction

Lung cancer is a common malignant tumor of the respiratory system and leads in both incidence and mortality rates among cancers in China. According to global cancer statistics in 2020, there were as many as 2.2 million new cases of lung cancer worldwide. The incidence rate of lung cancer in China is approximately 58.4 per 100,000, and the mortality rate is about 46.8 per 100,000, with the incidence showing an increasing trend year by year [1][2][3][4]. Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for about 85% of all lung cancer cases[5][6][7]. The standard treatments for lung cancer include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy[8][9][10]. However, these treatment regimens are only effective for patients with early-stage NSCLC (stages I-II) and are associated with certain adverse reactions. For patients diagnosed with advanced stages, the 5-year survival rate is less than 15% due to recurrence and metastasis. Therefore, in addition to enhancing the early diagnosis of lung cancer, exploring more effective therapeutic drugs related to the molecular mechanisms involved in lung cancer progression is of great significance for improving the prognosis of patients with lung cancer[11][12][13].

In recent years, traditional Chinese medicine (TCM) has played an important role in the treatment of tumors due to its unique advantages. It has attracted attention for its benefits in inhibiting tumor cell proliferation and metastasis, improving patient symptoms, enhancing quality of life, and reducing the toxic side effects of radiotherapy and chemotherapy. Currently, a variety of Chinese herbal formulas and proprietary Chinese medicines with anti-tumor effects are widely used in clinical practice and have shown good therapeutic effects on tumor patients. Traditional Chinese medicine contains a variety of components and targets, playing a significant role in regulating cancer cell proliferation, apoptosis, invasion, and metastasis, as well as inhibiting tumor angiogenesis, suppressing tumor growth, reducing chemotherapy adverse reactions, and lowering drug resistance. With the deepening of molecular biology research on the pathogenesis of lung cancer, various signaling pathways inducing lung cancer have attracted widespread attention [14][15][16][17]. The use of traditional Chinese medicine to regulate these signaling pathways in the intervention of lung cancer has been actively explored by many researchers. Studies have found that traditional Chinese medicine can regulate cell proliferation and apoptosis, modulate matrix metalloproteinases (MMPs) to inhibit cell migration, suppress angiogenesis, inhibit lung cancer epithelial-mesenchymal transition (EMT), and induce cell autophagy by modulating classic signaling pathways such as phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt), nuclear factor-kappa B (NF-κB), secretory glycoprotein/β-catenin (Wnt/β-catenin), and mitogen-activated protein kinase (MAPK), thus exerting anti-lung cancer effects [18][19][20]. As there is currently a lack of related literature reviews, this article systematically summarizes the regulatory effects of traditional Chinese medicine on lung cancer-related signaling pathways, aiming to provide a scientific basis and reference for elucidating the molecular mechanisms of lung cancer development and exploring new diagnostic and treatment strategies for lung cancer intervention using traditional Chinese medicine.

2. NF-κB Signaling Pathway

2.1. NF-κB Signaling Pathway and Lung Cancer

The NF-κB signaling pathway was discovered in 1986, and its components include p50, p52, p65, RelB, and c-Rel. The NF-κB signaling pathway is divided into three types: the classical pathway, the non-classical pathway, and other pathways. The classical pathway is mainly activated by interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α), and it relies on the phosphorylation of IκB mediated by the IKK complex (IKKα, IKKβ, IKKγ), leading to the ubiquitination and degradation of IκB [21][22][23]. This process allows the p50/p65 NF-κB to enter the cell nucleus to regulate genes, thereby controlling the expression of TNFα, LPS (Lipopolysaccharide), BCL-2, etc., and influencing cell apoptosis and inflammation. The non-classical pathway is mainly activated by factors such as B cell-activating factor (BAFF) and lipoteichoic acid (LTA), and it relies on the activation of p52 mediated by IKKα, which allows the p52/RelB NF-κB dimer to enter the nucleus and regulate genes[24][25][26].

The role of the NF-κB signaling pathway in NSCLC is bidirectional. On one hand, it can enhance immunity; on the other hand, the activation of NF-κB by TNFα and IL-1 can lead to inflammation[27][28][29]. Reviewing the role of NF-κB in NSCLC-related cellular apoptosis, angiogenesis, EMT, metastasis, and stemness reveals mechanisms such as: NF-κB signaling pathway activation of Bcl-2 expression, inhibiting lung cancer cell apoptosis; regulation of MMPs expression, degrading the extracellular matrix, promoting tumor

metastasis and invasion; upregulation of VEGF and its receptors, promoting tumor angiogenesis.

2.2. Traditional Chinese Medicine Treating Lung Cancer through the NF-κB Signaling Pathway

One study used Astragalus polysaccharide (APS) subcutaneous injection in mice with lung cancer. After treatment, the expression of Toll-like receptor 4 (TLR4), myeloid differentiation factor (MyD88), and NF-κB p65 protein and mRNA in mice was reduced, tumor growth was inhibited, and immune function was enhanced [30][31][32].

Resveratrol is a non-flavonoid polyphenolic organic compound found in common traditional Chinese medicines such as Polygonum cuspidatum and Cassia seed. After treating A549 cells with resveratrol, the expression of NF-κB mRNA in the cells was reduced to 29.72% of the total mRNA, and the proliferation of A549 cells was inhibited in a time- and dose-dependent manner.

Geniposide, also known as Gardenoside, has antipyretic, analgesic, anti-inflammatory, and antithrombotic effects [33][34]. After treating H1975 cells with geniposide, the expression of silent information regulator 1 (SIRT1) protein increased, the expression of downstream protein NF-κB decreased, and cell viability, number of invasive cells, and cell migration rate were inhibited in a dose-dependent manner. This suggests that the anti-cancer effect of geniposide is related to the regulation of the SIRT1/NF-κB signaling pathway.

Magnolol is an extract from the traditional Chinese medicine Magnolia officinalis, with anti-inflammatory, anti-ulcer, and anti-tumor effects. Studies have found that magnolol can inhibit the growth and metastasis of lung cancer cells by suppressing VEGF expression through the NF-κB pathway, reducing angiogenesis in large cell lung cancer [35][36][37].

Artemisinin (ART) is a derivative of artemisinin, playing an important role in inducing apoptosis and inhibiting tumor metastasis. ART can inhibit the expression of tumor necrosis factor receptor-associated factor (TRAF) in the downstream NF-κB pathway of lung cancer xenografts in mice, suppressing lung cancer cell proliferation and xenograft growth.

3. MAPK Signaling Pathway

3.1. MAPK Signaling Pathway and Lung Cancer

The MAPK pathway plays a crucial role in cellular proliferation, differentiation, apoptosis, stress response, angiogenesis, and tumor metastasis. There are four cascades within the MAPK pathway: extracellular signal-regulated kinase (ERK), JNK, p38 MAPK, and ERK5. The signal transduction of these cascades relies on the activation of three to five layers of protein kinases, including MAP4K, MAP3K, MAPKK, MAPK, and MAPKAPK.

The impact of the MAPK pathway on lung cancer is primarily manifested in lung development, cellular apoptosis, tumor metastasis, and angiogenesis [38][39][40]. NSCLC has a strong correlation with p38 MAPK and STAT3, with high expression of p38 MAPK and STAT3 in NSCLC patients. Among the four cascades of MAPK, the ERK pathway is closely related to lung cancer. Concurrently, mutations or inactivation of the Mek gene encoding ERK can lead to incomplete lung development, tracheal cartilage malformation, and neonatal death. ERK can also promote the degradation of the extracellular matrix of lung cancer cells, and the invasiveness of lung cancer increases after ERK activation [41][42][43]. Additionally, the p38 MAPK pathway in MAPK is also related to lung cancer. p38 MAPK can promote tumor angiogenesis by activating HIF-1 and affecting the transcription of VEGF, thereby facilitating lung cancer metastasis. Studies have also found that p38 MAPK undergoes phosphorylation after being treated with reactive oxygen species (ROS), inducing apoptosis in lung cancer cells.

3.2. Traditional Chinese Medicine Treating Lung Cancer through the MAPK Signaling Pathway

Leonurine, derived from motherwort, can enhance the vitality of phagocytes, interfere with cellular metabolism, and inhibit tumor growth. Salidroside can inhibit tumor proliferation by suppressing the MAPK signaling pathway, reducing the expression of phosphorylated extracellular signal-regulated kinase 1/2 (p-ERK1/2), c-Myc, and cyclin D1 [44][45].

The active saponin Paris saponin II, found in the traditional Chinese medicine Paris polyphylla, has anti-inflammatory, antiviral, and blood pressure-lowering effects. Camptothecin is a plant-derived anticancer drug. The combined treatment of Paris saponin II and camptothecin on H446 cells can promote the phosphorylation of p38 MAPK and ERK, downregulate

the expression of Bcl-2 and Bcl-XL proteins, and significantly increase the early apoptosis rate of lung cancer cells, a process that may be mediated by apoptosis induced by the affected mitochondrial signaling pathway.

Paeonol, derived from the traditional Chinese medicine Paeonia suffruticosa, can inhibit the expression of p-ERK in A549 cells and shows concentration-dependent inhibition of the secretion of matrix metalloproteinase family proteins MMP-2 and MMP-9 [46][47][48]. It enhances the adhesion capacity of the extracellular matrix to tumor cells and inhibits the migration and invasion abilities of lung cancer cells.

4. Monomeric Traditional Chinese Medicine Reversing Multidrug Resistance in NSCLC and Its Mechanisms

Non-small cell lung cancer (NSCLC), characterized by high mortality and recurrence rates, has undergone various treatment strategies, including personalized chemotherapy and radiotherapy. Despite initially favorable clinical responses, almost all patients with a treatment response eventually develop varying degrees of chemotherapy resistance within a year, thereby affecting treatment outcomes. Thus, inherent or acquired tumor cell resistance is a major obstacle to effective chemotherapy in NSCLC. Recent studies have found that active monomeric components in certain traditional Chinese herbs have a significant inhibitory effect on resistance, and some can even reverse multidrug resistance [49][50]. Traditional Chinese medicine, particularly active monomeric components, has always been favored by researchers for its multi-target, low toxicity, and cost-effectiveness. This article will summarize the research findings on the reversal of multidrug resistance in NSCLC treatment by active monomeric components of traditional Chinese medicine and discuss the research prospects for reversing multidrug resistance in lung cancer.

4.1. Triptolide

Triptolide (TPL) is a diterpenoid compound isolated and purified from the traditional Chinese herb Tripterygium wilfordii. An increasing number of clinical studies have found that TPL possesses strong antitumor activity and has good potential in reversing resistance. As an adjuvant antitumor drug, TPL can enhance the therapeutic effect of low-dose anticancer drugs such as camptothecin and increase the sensitivity of resistant cells to chemotherapeutic drugs. Some studies have found that the combination of TPL and gefitinib can synergistically inhibit the migration and invasion of A549 cells, and the combined treatment is significantly more effective than the individual treatments of TPL and gefitinib. At the same time, TPL can also enhance the sensitivity of resistant A549 cells to gefitinib by upregulating the expression of E-cadherin and downregulating the levels of MMP9, SNAIL, and vimentin [51][52][53]. Administering TPL can promote apoptosis and cell cycle regulation in paclitaxel-resistant lung adenocarcinoma cells (A549/Taxol). TPL exerts its effects in the reversal of paclitaxel resistance by inhibiting the NF-κB signaling pathway and the transcription and expression of resistance genes regulated by it, including FLICE-like inhibitory protein, X-linked inhibitor of apoptosis, Bcl-2, Bcl-xL, and cyclooxygenase-2, with dose and time dependency. Recent studies have found that the Kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 (Keap1/Nrf2) pathway is closely related to cancer progression and chemoresistance, making antagonizing Nrf2 a viable strategy in cancer treatment. Concurrently, studies have found that TPL can significantly inhibit the expression and transcriptional activity of Nrf2 in various NSCLC cells.

4.2. Curcumin

Curcumin (Cur) is a class of compounds widely found in the roots and stems of traditional Chinese medicinal herbs such as turmeric, goji berry, and sweet flag. Cur has a broad pharmacological profile, and modern research indicates that it possesses lipid-lowering, antitumor, anti-inflammatory, and antioxidant effects, and can even inhibit the development of cancer at all stages. As a chemosensitizer in tumor treatment processes, Cur also serves as a chemoradiotherapy protective agent for normal tissues and organs [54][55]. Cisplatin (DDP) is one of the most commonly used chemotherapeutic drugs for treating malignancies, including lung cancer, but its effectiveness is often diminished by the acquired resistance of tumor cells. Current research suggests that the abnormal activation of the Nrf2 pathway and autophagy induced by DDP is an important cause of resistance in A549/DDP cells. Cur's effective activation of Keap1 transcription weakens this process and counters resistance, which is crucial for the interaction between oxidative stress-induced Nrf2 activation and the autophagy/apoptosis switch. Experiments with transient transfection and flow cytometry revealed that the abnormality of

Hypoxia-inducible factor 1 (HIF-1) leads to DDP resistance in A549/DDP lung cancer cells. Combined treatment with Cur and DDP significantly inhibits the proliferation of A549/DDP cells by promoting the degradation of HIF-1 and activating caspase-3, reversing DDP resistance, and inducing apoptosis. DDP primarily prevents cancer cell DNA replication by producing intrastrand and interstrand DNA crosslinks, thereby killing cancer cells. At the same time, Cur enhances the proliferation inhibition and apoptosis of A549/DDP cells induced by DDP by inhibiting the Fanconi anemia/BRCA DNA repair pathway, suggesting that Cur can act as a chemosensitizer for the crosslinking anticancer drug DDP, reversing the resistance of DDP-resistant lung cancer cells to DDP. Further research indicates that Cur alters the expression of miRNAs in tumor cells, particularly by significantly downregulating the expression of miR-186* in A549/DDP, thereby exerting its anticancer effect on multidrug-resistant A549/DDP. Carboplatin, an analog of DDP with a similar mechanism of action but lower toxicity, is widely used in the treatment of various cancers. However, the one-year survival rate for patients with advanced NSCLC using carboplatin is only 40%–50%, and the activation of survival signaling pathways and induction of multidrug resistance by chemotherapy are the main reasons for this outcome. Studies show that the synergistic antitumor activity of Cur combined with carboplatin is mediated by multiple mechanisms, involving the inhibition of the Akt/IKKa pathway and the enhancement of ERK1/2 activity, thereby suppressing NF-κB. Therefore, Cur has the potential to become a chemosensitizer for carboplatin and to treat NSCLC.

4.3. Ginsenoside Rg3

Ginsenoside Rg3 (Rg3) is a steroidal saponin isolated from ginseng. Modern research has found that Rg3 can enhance the efficacy of chemotherapy. Gemcitabine (GEM) is a chemotherapeutic drug used to treat advanced NSCLC, but its effectiveness is poor; many patients experience adverse reactions to treatment, showing chemotherapy resistance, and the disease further progresses. Rg3 can eliminate ROS-mediated Akt activation and the activation of the extracellular signal-regulated kinase (ERK) pathway induced by GEM, and inhibit the nuclear accumulation of nuclear factor NF-κB and HIF-1α. Studies have shown that Rg3 can inhibit the growth of A549/DDP cells, reduce the expression of PD-L1 induced by chemotherapy resistance, restore the cytotoxicity of T cells to cancer cells, thereby reducing its resistance to DDP, and thus, Rg3 is expected to become a new drug targeting PD-L1 in chemoresistant NSCLC. Research has found that Rg3 increases the sensitivity of A549/DDP cells to DDP by downregulating proteins mediated by multidrug resistance, including P-glycoprotein (P-gp), multidrug resistance protein-1 (MPR1), and lung resistance protein 1, reversing the multidrug resistance of lung cancer patients. The Nrf2 signaling pathway mainly regulates oxidative stress responses, and in many types of cancer, high constitutive expression of Nrf2 leads to tumor cell proliferation and resistance. Some studies have found that ginsenoside Rd (Rd) inhibits the proliferation of A549 cells and induces G0/G1 phase arrest; Nrf2 plays an important role in the acquired resistance of NSCLC, and Rd may improve this resistance by downregulating the Nrf2 pathway[56][57]. Ginsenoside Rg5 (Rg5) belongs to the original panaxadiol ginsenosides, and recent research has found that Rg5 overcomes P-gp-mediated resistance by inhibiting the P-gp transporter and the chemotherapy resistance-related AKT/Nrf2 pathway, and Rg5 does not affect the expression of the P-gp transporter. Actinomycin D (ActD) is an anticancer drug that blocks DNA-dependent transcription and inhibits topoisomerase, causing DNA double-strand breaks, avoiding ActD resistance in lung cancer cells, and improving therapeutic effects.

4.4. Leonurine

Leonurine is a natural compound extracted from the herb Leonurus japonicus, and leonurine injection has been widely used in the treatment of various malignant tumors, including lung cancer, liver cancer, gastrointestinal malignancies, bladder cancer, and more. Recent studies have shown that leonurine can reverse the resistance of tumor cells and is promising as a novel anti-multidrug resistance therapeutic drug for the treatment of malignant tumors. Molecular targeted therapy is a promising strategy for treating patients with NSCLC. Molecular targeted drugs such as erlotinib have shown good clinical efficacy in advanced NSCLC, but patients inevitably develop resistance after 8 to 12 months of effective treatment, leading to tumor recurrence or metastasis and treatment failure. Recent research has found that leonurine can reverse the resistance of human NSCLC cells to erlotinib in vitro by reducing the expression of P-gp, inhibiting the P-gp-dependent extrusion, and increasing the intracellular concentration of anticancer drugs. Consistent with its role in activating apoptosis, leonurine inhibits the proliferation of A549/DDP cells in a time- and dose-dependent manner by reducing the mitochondrial membrane potential of tumor cells, increasing the

concentration of intracellular reactive oxygen species, and other pathways. Additionally, leonurine enhances the sensitivity of A549/DDP cells to DDP, reversing the resistance of A549/DDP cells.

4.5. Other Active Monomers of Traditional Chinese Medicine

The human lung adenocarcinoma PC14 cells, which lack EGFR mutations, are less sensitive to gefitinib than PC9 cells with EGFR mutations. Tetrandrine can increase the sensitivity of PC14 cells to gefitinib by inhibiting lysosomal function. Tetrandrine, in combination with DDP, can induce autophagy, reduce the viability of both DDP-resistant and DDP-sensitive A549 cells, and reverse the resistance of A549 cells to DDP. Therefore, tetrandrine is an effective autophagy agonist and may be a promising drug for the treatment of NSCLC. Recent studies in in vivo experiments with a mouse xenograft model found that the combined treatment of tangeretin and doxorubicin can significantly reduce tumor volume by 84.15%. Data show that tangeretin can enhance the cytotoxicity of A549/doxorubicin cells induced by doxorubicin by inhibiting the expression of MRP1, suggesting that it can serve as an effective adjuvant for doxorubicin chemotherapy in lung cancer. Emodin significantly enhances the growth-inhibitory effect of DDP in A549/DDP cells, and its combined use with DDP can effectively promote apoptosis in lung cancer cells and inhibit cell migration and invasion, which may be related to the inhibition of the NF-κB pathway [58][59]. Parthenolide (PN) is an active component of feverfew, which has long been used to treat inflammation, migraines, menstrual disorders, fever, and rheumatoid arthritis. PN can reverse doxorubicin resistance by inhibiting NF-κB activation and upregulating HSP70, thereby suppressing the expression of P-gp. The endogenous expression of Nrf2 and its target genes GCLC, GCLM, HO-1, NQO1, MRP1 in A549/DDP cells is much higher than in A549 cells, and silencing Nrf2 can partially restore the sensitivity of A549/DDP cells to DDP. Research has found that compared to treatment with DDP alone, the combined use of tanshinone and DDP can sensitize A549/DDP cells to DDP, leading to their death and apoptosis. Specifically, tanshinone reduces the expression of Nrf2, thereby leading to a decrease in the expression of its target genes, reversing the chemotherapy resistance of lung cancer cells to DDP. In summary, traditional Chinese medicine has great potential in reversing lung cancer resistance, but most of the related research is currently only at the in vitro level, and there is still a long way to go before clinical application.

5. Conclusion

Lung cancer poses a considerable threat to global human health and life safety, with over 50% of patients being diagnosed at an advanced stage, which directly results in a scarce chance of cure through surgical resection. Currently, chemotherapy and radiotherapy are the main treatment methods for lung cancer, but due to their significant toxic side effects and the easy development of resistance, patients find it difficult to adhere to treatment, leading to low cure rates and high recurrence rates. In recent years, traditional Chinese medicine has attracted researchers' attention due to its strong pharmacological activity, minimal toxic side effects, and the advantage of multi-targeted combined treatment for tumors. The active components of traditional Chinese medicine that are currently studied against NSCLC mainly include alkaloids, saponins, terpenes, polysaccharides, etc., all of which have shown inhibitory effects on NSCLC proliferation. When combined with radiotherapy and chemotherapy, they can effectively reduce the recurrence and metastasis rates, reverse multidrug resistance, and improve treatment efficiency. Since ancient times, traditional Chinese medicine has emphasized that humans are an organic whole with strong self-healing capabilities, advocating for enhancing the body's own immune system to combat cancer cells. This is consistent with the current research focus on immunotherapy. Chinese herbal formulas start from improving immune function, reducing adverse reactions to chemotherapy, and improving the quality of life, thereby comprehensively enhancing the treatment effects for lung cancer.

Statements and Declarations

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

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

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References

1. ^ *You Y, Chen Y, Zhang Q, Yan N, Ning Y, Cao Q. Muscle quality index is associated with trouble sleeping: a cross-sectional population based study. BMC Public Health. 2023;23(1):489.*
2. ^ *Su X L, Wang J W, Che H. Clinical application and mechanism of traditional Chinese medicine in treatment of lung cancer. Chinese Medical Journal, 2020, 133(24): 2987-2997.*
3. ^ *Li Z, Feiyue Z, Gaofeng L. Traditional Chinese medicine and lung cancer——From theory to practice. Biomedicine & Pharmacotherapy, 2021, 137: 111381.*
4. ^ *Wei Z, Chen J, Zuo F. Traditional Chinese Medicine has great potential as candidate drugs for lung cancer: A review. Journal of Ethnopharmacology, 2023, 300: 115748.*
5. ^ *Yang Z, Zhang Q, Yu L. The signaling pathways and targets of traditional Chinese medicine and natural medicine in triple-negative breast cancer. Journal of ethnopharmacology, 2021, 264: 113249.*
6. ^ *Tang C, Zhao C C, Yi H. Traditional Tibetan medicine in cancer therapy by targeting apoptosis pathways. Frontiers in Pharmacology, 2020, 11: 976.*
7. ^ *Wang S, Long S, Deng Z. Positive role of Chinese herbal medicine in cancer immune regulation. The American journal of Chinese medicine, 2020, 48(07): 1577-1592.*
8. ^ *Wen T, Song L, Hua S. Perspectives and controversies regarding the use of natural products for the treatment of lung cancer. Cancer Medicine, 2021, 10(7): 2396-2422.*
9. ^ *Sui X, Han X, Chen P. Baicalin induces apoptosis and suppresses the cell cycle progression of lung cancer cells through downregulating Akt/mTOR signaling pathway. Frontiers in Molecular Biosciences, 2021, 7: 602282.*
10. ^ *Zhang Q, Liu J, Li R. A network pharmacology approach to investigate the anticancer mechanism and potential active ingredients of Rheum palmatum L. against lung cancer via induction of apoptosis. Frontiers in Pharmacology, 2020, 11: 528308.*
11. ^ *Yang J, Zhu X, Yuan P. Efficacy of traditional Chinese Medicine combined with chemotherapy in patients with non-small cell lung cancer (NSCLC): a meta-analysis of randomized clinical trials. Supportive Care in Cancer, 2020, 28: 3571-3579.*
12. ^ *Zhao B, Hui X, Jiao L. A TCM formula YYWY inhibits tumor growth in non-small cell lung cancer and enhances immune-response through facilitating the maturation of dendritic cells. Frontiers in Pharmacology, 2020, 11: 798.*
13. ^ *Ding Z, Zhong R, Yang Y. Systems pharmacology reveals the mechanism of activity of Ge-Gen-Qin-Lian decoction against LPS-induced acute lung injury: a novel strategy for exploring active components and effective mechanism of TCM formulae. Pharmacological Research, 2020, 156: 104759.*
14. ^ *Wang N, Feng T, Liu X. Curcumin inhibits migration and invasion of non-small cell lung cancer cells through up-regulation of miR-206 and suppression of PI3K/AKT/mTOR signaling pathway. Acta pharmaceutica, 2020, 70(3): 399-409.*
15. ^ *Kong M, Li L, Lou Y. Chinese herbal medicines for prevention and treatment of colorectal cancer: from molecular mechanisms to potential clinical applications. Journal of integrative medicine, 2020, 18(5): 369-384.*
16. ^ *Zhang X, Qiu H, Li C. The positive role of traditional Chinese medicine as an adjunctive therapy for cancer. Bioscience trends, 2021, 15(5): 283-298.*
17. ^ *Fang C, Wang L, Gong C. Long non-coding RNAs: How to regulate the metastasis of non–small-cell lung cancer. Journal of cellular and molecular medicine, 2020, 24(6): 3282-3291.*
18. ^ *Jiang H, Li M, Du K. Traditional Chinese Medicine for adjuvant treatment of breast cancer: Taohong Siwu Decoction. Chinese medicine, 2021, 16: 1-20.*
19. ^ *Zhang B, Wu J, Guo P. Down-regulation of SREBP via PI3K/AKT/mTOR pathway inhibits the proliferation and invasion of non-small-cell lung cancer cells. OncoTargets and therapy, 2020: 8951-8961.*
20. ^ *Liao X Z, Gao Y, Zhao H W. Cordycepin reverses cisplatin resistance in non-small cell lung cancer by activating AMPK and inhibiting AKT signaling pathway. Frontiers in cell and developmental biology, 2021, 8: 609285.*
21. ^ *Wang K, Chen Q, Shao Y. Anticancer activities of TCM and their active components against tumor metastasis. Biomedicine & Pharmacotherapy, 2021, 133: 111044.*
22. ^ *Ali M, Wani S U D, Salahuddin M. Recent advance of herbal medicines in cancer-a molecular approach. Heliyon, 2023, 9(2).*
23. ^ *Wang Y, Zhang Q, Chen Y. Antitumor effects of immunity-enhancing traditional Chinese medicine. Biomedicine & Pharmacotherapy, 2020, 121: 109570.*
24. ^ *Liu Y, Yang S, Wang K. Cellular senescence and cancer: Focusing on traditional Chinese medicine and natural products. Cell proliferation, 2020, 53(10): e12894.*
25. ^ *Xu W T, Li T Z, Li S M. Cytisine exerts anti-tumour effects on lung cancer cells by modulating reactive oxygen species-mediated signalling pathways. Artificial Cells, Nanomedicine, and Biotechnology, 2020, 48(1): 84-95.*

26. ^Iksen, Pothongsrisit S, Pongrakhananon V. Targeting the PI3K/AKT/mTOR signaling pathway in lung cancer: an update regarding potential drugs and natural products. Molecules, 2021, 26(13): 4100.
27. ^Zhang Y, Lou Y, Wang J. Research status and molecular mechanism of the traditional Chinese medicine and antitumor therapy combined strategy based on tumor microenvironment. Frontiers in immunology, 2021, 11: 609705.
28. ^Yan X, Ying-Rong H U A, Shang J. Traditional Chinese medicine network pharmacology study on exploring the mechanism of Xuebijing Injection in the treatment of coronavirus disease 2019. Chinese journal of natural medicines, 2020, 18(12): 941-951.
29. ^Liao X, Bu Y, Jia Q. Traditional Chinese medicine as supportive care for the management of liver cancer: past, present, and future. Genes & diseases, 2020, 7(3): 370-379.
30. ^Xu L, Bi Y, Xu Y. Oridonin inhibits the migration and epithelial-to-mesenchymal transition of small cell lung cancer cells by suppressing FAK-ERK1/2 signalling pathway. Journal of cellular and molecular medicine, 2020, 24(8): 4480-4493.
31. ^Luo H, Gao Y, Zou J. Reflections on treatment of COVID-19 with traditional Chinese medicine. Chinese medicine, 2020, 15(1): 94.
32. ^You Y, Chen Y, Zhang Y, Zhang Q, Yu Y, Cao Q. Mitigation role of physical exercise participation in the relationship between blood cadmium and sleep disturbance: a cross-sectional study. BMC Public Health. 2023;23(1): 1465.
33. ^You Y, Chen Y, You Y, Q Zhang, Q Cao. Evolutionary Game Analysis of Artificial Intelligence Such as the Generative Pre-Trained Transformer in Future Education. Sustainability, 2023, 15(12): 9355.
34. ^You Y, Chen Y, Li J, Zhang Q, Zhang Y, Yang P, Cao Q. Physical activity mitigates the influence of blood cadmium on memory function: a cross-sectional analysis in US elderly population. Environmental Science and Pollution Research. 2023;30(26):68809-68820.
35. ^You Y, Chen Y, Chen X, Wei M, Yin J, Zhang Q, Cao Q. Threshold effects of the relationship between physical exercise and cognitive function in the short-sleep elder population. Frontiers in Aging Neuroscience. 2023;15:1214748.
36. ^Cao Q, Zhang Q, Chen YQ, Fan AD, Zhang XL. Risk factors for the development of hepatocellular carcinoma in Chengdu: a prospective cohort study. European Review for Medical and Pharmacological Sciences. 2022;26(24):9447-9456.
37. ^Cao Q, Zhang Q, Li XC, Ren CF, Qiang Y. Impact of sleep status on lung adenocarcinoma risk: a prospective cohort study. European Review for Medical and Pharmacological Sciences. 2022;26(20):7641-7648.
38. ^Cao Q, Zhang Q, Zhou KX, Li YX, Yu Y, He ZX, Xiang ZB, Guan HR, Zhen JC, Lin RT, Liao YJ, Qiang Y, Li XC. Lung cancer screening study from a smoking population in Kunming. European Review for Medical and Pharmacological Sciences. 2022;26(19):7091-7098.
39. ^Qiang C, Qi Z, Yi Q. Mechanisms of p2x7 receptor involvement in pain regulation: a literature review. Acta Medica Mediterranea, 2022, 38(2): 1187-1194.
40. ^Cao Q, Zhang Q, Chen Y Q, Li J X, Yi Q. The Association Between Unhealthy Weight Loss Behaviours and Depressive Symptoms in Adolescents: a Cross-Sectional Study. Advances in Education, Humanities and Social Science Research, 2022, 1(3): 237-237.
41. ^Cao Q, Zhang Q, Chen Y, He Z, Xiang Z, Guan H, Yan N, Qiang Y, Li M. The relationship between non-suicidal self-injury and childhood abuse in transgender people: a cross-sectional cohort study. Frontiers in psychology, 2023, 14: 1062601.
42. ^You Y, Chen Y, Zhang Q, Hu X, Li X, Yang P, Zuo Q, Cao Q. Systematic and meta-based evaluation of the relationship between the built environment and physical activity behaviors among older adults. PeerJ, 2023, 11: e16173.
43. ^Cao Q, Ye X, Wu X, Zhang Q, Gong J, Chen Y, You Y, Shen J, Qiang Y, Cao G. Therapeutic efficacy of rare earth carbonate with chemoradiotherapy in late-stage non-small cell lung cancer: a cohort prospective study. Frontiers in Endocrinology, 2023, 14: 1301032.
44. ^Cao Q, Zhu J, Wu X, Li J, Chen Y, You Y, Li X, Huang X, Zhang Y, Li R, Han D. Efficacy and Safety Assessment of Intrathoracic Perfusion Chemotherapy Combined with immunological factor Interleukin-2 in the Treatment of Advanced Non-Small Cell Lung Cancer: A Retrospective Cohort Study. J Cancer 2024; 15(7):2024-2032.
45. ^Cao Q, Wu X, Zhang Q, Gong J, Chen Y, You Y, Shen J, Qiang Y, Cao G. Mechanisms of action of the BCL-2 inhibitor venetoclax in multiple myeloma: a literature review. Frontiers in Pharmacology, 2023, 14: 1291920.
46. ^Cao Q, Wu X, Chen Y, Wei Q, You Y, Qiang Y, Cao G. The impact of concurrent bacterial lung infection on immunotherapy in patients with non-small cell lung cancer: a retrospective cohort study. Frontiers in cellular and infection microbiology, 2023, 13: 1257638.
47. ^Wu X, Zhou Z, Cao Q, Chen Y, Gong J, Zhang Q, Qiang Y, Lu Y, Cao G. Reprogramming of Treg cells in the inflammatory microenvironment during immunotherap

y: a literature review. Frontiers in immunology, 2023, 14: 1268188.

48. ^*You Y, Chen Y, Wang X, Wei M, Zhang Q, Cao Q. Accelerometer-measured physical activity patterns are associated with phenotypic age: Isotemporal substitution effects. Heliyon, 2023, 9(9):e19158.*
49. ^*Cao Q, Wang Q, Wu X, Zhang Q, Huang J, Chen Y, You Y, Qiang Y, Huang X, Qin R, Cao G. A literature review: mechanisms of antitumor pharmacological action of leonurine alkaloid. Frontiers in pharmacology, 2023, 14: 1272546.*
50. ^*You Y, Wei M, Chen Y, Fu Y, Ablitip A, Liu J, Ma X. The association between recreational physical activity and depression in the short sleep population: a cross-sectional study. Frontiers in Neuroscience, 2023, 17: 1016619.*
51. ^*Chen YQ, Zhu XL, You YW, Zhang Q, Dai T. Evaluation of status quo and determinants of catastrophic health expenditure among empty-nest elderly in China: evidence from the China health and retirement longitudinal survey (CHARLS). European review for medical and pharmacological sciences, 2023, 27(4): 1398-1412.*
52. ^*Chen YQ, You YW, Zhang Q, Wang YD, Dai T. Systematic evaluation of influencing factors for Chinese rural doctors' job satisfaction and turnover intention: based on the two-factor theory. European review for medical and pharmacological sciences, 2022, 26(18): 6469-6486.*
53. ^*Chen Y, You Y, Wang Y, Wang Y, Dai T. Global insights into rural health workers' job satisfaction: a scientometric perspective. Frontiers in public health, 2022, 10: 895659.*
54. ^*Zheng HQ, Ma YC, Chen YQ, Xu YY, Pang YL, Liu L. Clinical analysis and risk factors of bronchiolitis obliterans after Mycoplasma Pneumoniae pneumonia. Infection and Drug Resistance, 2022: 4101-4108.*
55. ^*Xu J, Chen Y, Yue M, Yu J, Han F, Xu L, Shao Z. Prevalence of Neisseria meningitidis serogroups in invasive meningococcal disease in China, 2010-2020: a systematic review and meta-analysis. Human Vaccines & Immunotherapeutics, 2022, 18(5): 2071077.*
56. ^*Chen Y, You Y, Wang Y, Wang Y, Dai T. Systematic and meta-based evaluation on job satisfaction of village doctors: An urgent need for solution issue. Frontiers in Medicine, 2022, 9: 856379.*
57. ^*Zheng H, Yu X, Chen Y, Lin W, Liu L. Effects of Inhaled Corticosteroids on Lung Function in Children With Post-infectious Bronchiolitis Obliterans in Remission. Frontiers in Pediatrics, 2022, 10: 827508.*
58. ^*You Y, Chen Y, Fang W, Li X, Wang R, Liu J, Ma X. The association between sedentary behavior, exercise, and sleep disturbance: A mediation analysis of inflammatory biomarkers. Frontiers in Immunology, 2023, 13: 1080782.*
59. ^*Hu X, Chen Y, Shen Y, Tian R, Sheng Y, Que H. Global prevalence and epidemiological trends of Hashimoto's thyroiditis in adults: A systematic review and meta-analysis. Frontiers in Public Health, 2022, 10: 1020709.*

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