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Progress of Chinese Medicine Monomers and Combinations in Intervening Gefitinib Resistance in Non-small Cell Lung Cancer

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Abstract: ***Lung cancer is one of the common malignant tumors in clinic, among which the incidence of NSCLC accounts for about 85%, and the effect of the EGFR-TKI drug represented by gefitinib in the treatment of NSCLC is remarkable in clinic, but the acquired drug resistance is However, acquired drug resistance is one of the important reasons affecting the efficacy of gefitinib. In recent years, many studies have found that traditional Chinese medicine (TCM) can improve the sensitivity of lung cancer cells to gefitinib, and this paper focuses on the mechanism of TCM monomers and combinations in reversing the resistance to gefitinib from the aspects of increasing the concentration of intracellular drugs, inducing apoptosis of drug-resistant cells and inhibiting the signaling pathway of NSCLC, with the aim of providing a reference to find safe and effective reversal of drug resistance agents.***

Keywords: Lung cancer, Traditional Chinese medicine, Targeted therapy.

1. Introduction

Lung cancer threatens human life as a major global public health safety threat, and according to the National Cancer Center, the incidence and mortality of lung cancer are in the first place [1] Lung cancer is divided into small cell lung cancer and non-small cell lung cancer. Lung cancer is divided into small cell lung cancer and non-small cell lung cancer, of which non-small cell lung cancer accounts for 85% of all cases [2]. Non-small cell lung cancer accounts for 85%. Most of the lung cancer patients are diagnosed in middle or late stage, losing the chance of surgery. Chemotherapy and immunotherapy bring certain chance and time for most patients, but for non-small cell driver gene positive patients, targeted therapy is still their standard first-line treatment plan and has a milestone significance. EGFR-TKI drugs represented by gefitinib are widely used in the clinic, but patients treated with gefitinib tend to develop acquired resistance after 6-12 months, which severely limits the clinical efficacy of gefitinib treatment. Chinese herbal medicines contain a variety of active ingredients, which can act on all aspects of gefitinib resistance formation with the unique advantages of multi-target, multi-pathway, and personalization, effectively reversing gefitinib resistance and bringing significant clinical benefits to non-small cell patients. In this paper, we summarize and analyze the relevant literature reports on the intervention of traditional Chinese medicine monomers and combinations in gefitinib resistance in non-small cell lung cancer, and review the mechanism of resistance reversal, with a view to providing a new scientific basis for the subsequent research and clinical application.

1.1 Increase NSCLC Intracellular Drug Concentration

Blocking or restricting drug entry into the site of action through physical mechanisms is one of the most direct mechanisms by which tumors become resistant to drug therapy, mainly including increased drug efflux and decreased drug uptake. ATP (ATP-binding cassette (ABC) protein binding cassettes, such as P-Glycoprotein (P-GP), Multidrug Resistance-Related Protein-1 (MRP1), Lung Resistance Protein (LRP), Breast Cancer Resistance Protein (BCRP) and other transmembrane transport proteins are responsible for regulating the distribution, absorption and excretion of small molecules of drugs. (P-GP), multidrug resistance-associated protein-1 (MRP1), lung resistance protein (LRP), breast cancer resistance protein (BCRP), and other transmembrane transport proteins are responsible for regulating the distribution, absorption, and excretion of small molecules of drugs, and their aberrant expression can directly affect the drug concentration, affecting treatment and prognosis. Several studies have confirmed that TCM can increase the concentration of targeted drugs in lung cancer cells by regulating the expression of various transmembrane transporter proteins and effectively reverse drug resistance. Cellular energy metabolism maintains the most basic activities of living organisms, and the 2 main sources of ATP production are glycolysis and organic phosphorylation. Tumor cells excrete drugs out of the cell through ATP-dependent transporter proteins is one of their important reasons for drug resistance. Ai Xinyi et al. [3] found that the combination of comfreyatin and gefitinib not only increased the accumulation in HCC827/GR cells, inhibited the rate of cellular oxygen consumption and the rate of glycolytic proton efflux, and down-regulated the PKM2, p-EGFR, P-gp, and HIF-1α protein overexpression, but also interfered with the energy metabolism pathway of HCC827/GR cells, blocked the energy source of P-gp in the lung cancer cells, and limited the function of its pump, which in turn D-luciferin potassium salt is a specific substrate for the ABC transporter BCRP [4]. found that gefitinib combined with elemene increased PC-9/GR cellular uptake, and the AUC0-55 min and Cmax ($P<0.01$) of D-luciferin potassium salt in its treatment group were significantly higher than those in the control group, which inhibited cellular efflux, and thus resulted in an increase in the drug concentration. Fang Xupeng et al. [5] found that Yanningfang could inhibit the proliferation of lung adenocarcinoma H1975 cells, inhibit the activity of PI3K/AKT/m TOR in the downstream signaling pathway of

EGFR, and increase the sensitivity of H1975 cells to gefitinib, thus prolonging the effective period of the drug. Zhang Yi et al. [6] found that Jinfukang Oral Liquid combined with gefitinib inhibited glycolysis and increased the sensitivity of lung cancer drug-resistant cells by down-regulating the activity and expression level of key rate-limiting enzymes of the glycolytic pathway, HK2, PFKP, and PKM2, and by decreasing the content of ATP and lactate.

1.2 Induction of Apoptosis in Lung Cancer Resistant Cells

Abnormal apoptotic signaling is one of the important mechanisms of drug resistance in lung cancer cells, and aberrant expression of BCL-2, BAX, and the cysteoaspartic enzyme protein family contributes to drug resistance in lung cancer cells [7,8] Wang Chen-Chen Chenchen Wang [9] Andrographolide combined with GEF was found to significantly inhibit gefitinib-resistant strain of PC-9/GR human lung adenocarcinoma cells. Du Jiangyuan et al. [10] found that toxic carotenoids combined with gefitinib could further promote apoptosis in PC9/GR cells, and the mechanism was related to the endoplasmic reticulum ERS state of PC9/GR cells after the combination of drugs. Astragalus polysaccharide is an active ingredient of the Chinese herb Astragalus membranaceus [11]. Astragali polysaccharide combined with gefitinib was found to inhibit the invasion and migration ability of PC9/GR and HCC827/GR cells and induce apoptosis, thus reversing acquired resistance, and the mechanism was closely related to the inhibition of TLR4 expression. Wang Zhihong [12] It was found that Sijunzi Tang combined with different concentrations of gefitinib had a synergistic effect, which was able to increase the sensitivity of PC9 and PC9/GR cells to gefitinib, and regulate the important targets on glutamine metabolism (SLC1A5, GLS, and GS) affecting the changes in the content of metabolic markers related to glutamine metabolism, improving the acquired resistance, and causing the down-regulation of BCL -2 expression down-regulated and BAX expression up-regulated, promoting apoptosis in tumor cells. The main active ingredient of Conlette Injection is the oil of Coix lacryma extracted from the traditional Chinese medicine Coix lacryma, Gaoxin [13] It is found that Kanglet injection combined with gefitinib can inhibit the proliferation of H1299 cells, a gefitinib-resistant strain of non-small cell lung cancer, and induce apoptosis of human lung adenocarcinoma H1299 cells by inhibiting the expression of Bcl-2 and up-regulating the expression of Bax, thus reversing the resistance to the drug. Curcumin is a natural phenolic antioxidant extracted from the rhizomes of Curcuma longa, Curcuma longa and Ulmus, family Zingiberaceae, Sheng Qi et al. [14] Sheng Qi et al. found that curcumin combined with gefitinib could down-regulate the expression level of PI3K, activate the downstream apoptosis-related protein Caspase-3, and cause apoptosis, thus reversing gefitinib resistance. Zhang Weiping et al. [15] found that curcumin combined with gefitinib could down-regulate the levels of p-PI3K, p-Akt, p-Ras, p-ERK proteins, inhibit the phosphorylation levels of PI3K-Akt and RasRaf-MEK-ERK pathway in NCI-H1975 cells, and reverse the drug resistance. Triptolide (TPL), a diterpenoid extracted and isolated from the traditional Chinese medicine Lei Gong Teng, has anti-inflammatory and anti-tumor efficacy, and has great potential in influencing drug resistance [16,17] Zhang Yi [18] TPL combined with gefitinib was found to downregulate the PI3K/Akt/mTOR pathway and autophagy induction, thereby inhibiting the proliferative activity of EGFR mutant NSCLC cells.

1.3 Inhibition of Signaling Pathways

EGFR receptor-mediated signaling pathway is one of the important pathways to regulate cellular value-added differentiation, however, aberrant expression of the signaling pathway will attenuate the efficacy of EGFR-TKI drugs, and even generate drug resistance, therefore, regulating the signaling pathway has also become an important target for reversing gefitinib resistance. Wu Jiahui [19] It was found that ophiopogonin H, an active ingredient extracted from ophiopogon seeds, as a Notch inhibitor, could effectively inhibit the Notch3 signaling pathway in vitro and in vivo, enhance the sensitivity of gefitinib to PC-9/GR in drug-resistant cells, increase the expression of pro-apoptotic proteins Cleaved-caspase-3 and Bax, inhibit the expression of anti-apoptotic protein Bcl-2, and induce resistance to EGFR-TKI. and induced apoptosis in drug-resistant cells. Li Guangda [20] It was found that the combination of Gefitinib with Guoben Abolishing Tumor Capsules Plus and Minus Formula interfered with Gefitinib resistance by regulating the MEK/ERK signaling pathway downstream of EGFR as well as up-regulating the expression levels of PI3 and S100A8. Total flavonoids of Trifolium is the active constituent of the tuberous roots of Trifolium cliff-climbing vine Tetrastigma hemsleyanum Diels et Gilg, family Vitis vinifera, which possesses pharmacological effects such as antitumor, anti-inflammatory, bacteriostatic, and immunomodulatory effects [21] He Jiaqi et al. [22] It was found that Trifolium pratense modulated the PTEN/PI3K/AKT pathway, thereby reversing the reversible resistance of A549/GR cells to GEF. Zhang Ting et al. [23] found that Nourishing Yin Detoxification Formula had proliferation inhibitory effect on drug-resistant strain PC9/R, and there was a quantitative effect relationship, which could increase the expression of PTEN and inhibit the phosphorylation of AKT, the key protein of p-AKT activation site Thr308 and Ser473 signaling pathway of PC9/R, and thus play a dual role of inhibiting the growth of tumors and reversing the resistance to the drug. Jue Zhang [24] It was found that Yiqi and Phlegm Removal Formula combined with gefitinib could inhibit the cell viability of EGFR-TKIs resistant cell lines, reduce the resistance of drug-resistant cells to gefitinib, block the cell cycle, and inhibit the tumor volume and tumor weight of drug-resistant nude mice with the mechanism of down-regulation of the PI3K/Akt/m TOR pathway and the up-regulation of autophagy. Toad toxin is one of the main activities of the traditional Chinese medicine toadstool and toad skin, and Kang Xiaohong et al. [25] found that toadpoxin combined with gefitinib increased its sensitivity ($P<0.01$), and at the same time blocked the EGFR-PI3k/Akt signaling pathway and inhibited the secondary mutation of EGFR-T790M, thus suppressing drug resistance. Zhi Mu, as a representative drug of heat-clearing medicine, has excellent therapeutic effects, and Yu Yaya et al. [26] Yu Ya Ya et al. found that it could regulate and up-regulate the level of mitochondrial ROS, thus promoting oxidative stress-induced cell death, reversing the abnormal activation of the PI3K/AKT pathway, and prolonging gefitinib resistance.

1.4 Change in Drug Target

Gefitinib resistance is mainly due to gene mutations and activation of the bypass pathway. The most common mechanism is the T790M mutation, in which methionine replaces threonine at position 790 of exon 20 on the EGFR, thereby altering the affinity for ATP and leading to therapeutic failure of EGFR-TKIs. Mutations in T790M are a major problem for first- and second-generation EGFR-TKI drugs. with an incidence of 50% of acquired resistance to EGFR-TKIs [27]. The incidence of T790M mutation is 50% of acquired resistance to EGFR-TKIS. Liu Hao et al. [28] found that Fuzheng detoxification formula combined with gefitinib inhibited gefitinib resistance by reducing T790M mutation and inhibiting c-Met amplification. As a traditional Chinese medicine with a long history and a wide range of applications, Picea abies is known as "Cephalotaxus", "Picea abies" and "Picea abies" in ancient times. Zhang Gao Chenxi et al. [29] found that the aqueous extract of Picea abies enhanced the inhibitory effect of gefitinib on the proliferation of H1975 and H820 cells, and inhibited the resistance to gefitinib caused by T790M mutation and c-MET amplification, and its mechanism was related to the inhibition of EGFR/PI3K/AKT pathway. Berberine, also known as berberine, is a class of amine compounds extracted from Berberis vulgaris and Phellodendron amurense. Zheng Fang [30] Berberine combined with gefitinib was found to inhibit the proliferation of NSCLC cells through the PDPK1/Sp1/DNMT1 signaling pathway and could synergistically inhibit the occurrence of EMT process in NSCLC cells through the LncRNA HOTAIR/miR-34a-5p/ Snail signaling pathway. Luo Yang et al. [24] found that the combination of phlegm removing and detoxification formula and gefitinib could increase the expression of E-cadherin protein, decrease the expression of Snail and vimentin, and inhibit the EMT process, thus resisting drug resistance. Zeng Chaopeng [31] Cucurbitacin B was found to inhibit the Jak2/STAT3 signaling pathway, thereby affecting EGFR activation mutations and reversing gefitinib resistance. Zang Chuanlong et al [27] found that Zhenwu Tang combined with Gefitinib in the treatment of spleen and kidney yang deficiency type of lung adenocarcinoma, 92 patients were randomly divided into two groups, and after using Zhenwu Tang for 12 weeks, it was found that it could reduce the occurrence of adverse reactions such as rash, diarrhea and so on, improve the quality of life, prolong the symptomatic survival, and has a high degree of safety.

2. Summary

EGFR-TKIs can selectively bind to the ATP-binding site of the tyrosine kinase domain in EGFR cells, block the phosphorylation and activation of tyrosine itself within the EGFR molecule through the pathway of AKT and MAPK, inhibit the downstream signaling pathways such as RAS/RAF/MAPK, PI3K-Akt, etc, so as to make the tumor cells apoptotic. EGFR-TKI drugs have the advantages of good efficacy and EGFR-TKI drugs have the advantages of good efficacy, small adverse reactions, convenience, etc., and are widely used in the clinic, but drug resistance is the yoke of the limitation of the efficacy of the targeted drugs. In recent years, in the extensive research on TCM, a large number of scholars believe that TCM can reverse the resistance mechanism of gefitinib, and also increase the efficacy and reduce the toxicity of gefitinib. In addition, the rest of the TCM therapeutic means (e.g., acupuncture, acupuncture point plastering and herbal rubbing, etc.) can also alleviate the patient's skin rashes and other adverse reactions.

Lung cancer belongs to the categories of Chinese medicine, such as "interest cardia", "lung accumulation", "labor cough", etc. According to "The Essentials of the Golden Chamber", it is recorded that "the patient's chest is full of impotence of the lips, the tongue is green and the mouth is dry, but wants to gargle water, does not want to swallow, there is no cold or heat". But want to gargle water, do not want to swallow, no cold and heat ..... for there is blood stasis". The disease is located in the lungs, which is closely related to the rest of internal organs. Chinese medicine believes that the etiology and pathogenesis of lung cancer are mostly deficiency, stasis, phlegm and toxicity, which is always the standard of this deficiency, and "the accumulation of wind-cold accumulation of the five viscera and the disease pulse evidence and treatment of the eleventh", "the accumulation of the disease, the disease of the viscera, the end of the unchanging", the feeling of cancerous venom, and the deficiency of positive qi and the seven emotions are out of order, so that the functions of the internal organs are out of order, and the disease-causing factors interact with each other to make phlegm and stasis of toxicity coagulation, qi and blood deficiency, and the ability of body to resist evil decreases in long-term development. The ability of resisting evil decreases, and the tumor is formed in the long term. Most of the symptoms are spleen deficiency, phlegm-dampness, deficiency of qi and yin, and qi stagnation and blood stasis [32,33]. In order to improve the intracellular drug concentration of NSCLC, induce apoptosis of drug-resistant cells and inhibit the signaling pathway, Chinese medicine can reverse the drug-resistant mechanism and regulate the sensitivity of lung cancer cells to gefitinib, so as to make gefitinib more effective and effective [34]. In addition, the use of gefitinib often brings many adverse reactions, such as skin rash, diarrhea, etc., which seriously affects the life of patients, and many studies have shown that traditional Chinese medicine (TCM) can alleviate the adverse reactions and reduce the toxicity and side effects of patients [35,36]. However, the regulation of Gefitinib resistance by TCM is not a single mechanism, but multiple mechanisms, which need to be investigated by a large number of animal and clinical experiments in the future.

References

[1] He S, Xia C, Li H, et al. Cancer profiles in China and comparisons with the USA: a comprehensive analysis in the incidence, mortality, survival, staging, and attribution to risk factors[J]. Science China Life Sciences, 2023.

[2] Relli V, Trerotola M, Guerra E, et al. Abandoning the Notion of Non-Small Cell Lung Cancer[J]. Trends in Molecular Medicine, 2019, 25(7): 585-594.

[3] AI Xinyi, HOU Xuefeng, FENG Nianping. Reversal of drug resistance in human non-small cell lung cancer by combining comedicine and gefitinib and its mechanism [J]. Chinese Journal of Traditional Chinese Medicine, 2024, 49(1): 175-184.

[4] CHEN Zhi, YU Jiandong, TANG Chaoyuan, et al. Effects of elemene injection on the intracellular transport kinetics of gefitinib in PC-9/GR cells[J]. Chinese Patent Medicine, 2018, 40(2): 284-290.
[5] FANG Xupeng, FANG Dan, DANG Haibin, et al. Effects of Lung Yan Ning Fang combined with Gefitinib on the proliferation of lung adenocarcinoma H1975 cells in vitro[J]. Shanghai Journal of Traditional Chinese Medicine, 2022, 56(8): 79-83.
[6] ZHANG Yi, WANG Qiuyue, JIA Fang, et al. Effects of Jin Fu Kang oral solution combined with gefitinib on the growth and aerobic glycolysis of transplanted tumors in H1975 lung cancer nude mice[J]. Chinese Journal of Integrative Medicine, 2022, 42(2): 210-217.
[7] WANG Shiyi, LIU Tiexin, HE Chenjia, et al. Targeting Bcl-2 to overcome acquired resistance to EGFR-TKIs in non-small cell lung cancer[J]. Advances in Modern Biomedicine, 2023, 23(15): 2801-2808.
[8] Hu Yabin. N-acetylcysteine radicicolothionein inhibits autophagy through microtubule fracture leading to apoptosis in non-small cell lung cancer cells[D]. Beijing: Capital Medical University, 2018.
[9] Wang, Chen Chen. Andrographolide synergizes with gefitinib to overcome PC9/G cell resistance in non-small cell lung cancer [D]. Jinzhou Medical University, 2024.
[10] DU Jiangyuan, ZHANG Lanlin, CAI Tongkai, et al. Toxic carotenoids combined with gefitinib to improve drug resistance in human lung adenocarcinoma cells with PC9/GR[J]. Pharmacy Practice and Service, 2024, 42(3): 121-126.
[11] Zhuang Yaoxue. Mechanistic study on the reversal of acquired resistance to gefitinib in NSCLC by astragalus polysaccharide through TLR4 pathway [D]. Beijing University of Traditional Chinese Medicine.
[12] Wang Zhihong. Mechanism study on the improvement of gefitinib resistance by regulating glutamine metabolism with Sijunzi Tang [D]. Peking Union Medical College, 2023.
[13] Gao Xin. Effects of Kanglet injection combined with gefitinib on the proliferation and apoptosis of human lung adenocarcinoma cells[D]. Shenyang: Liaoning University of Traditional Chinese Medicine, 2020.
[14] Sheng Q, Chen J, Li M. Reversal of gefitinib resistance by curcumin in non-small cell lung cancer[J]. China Modern Applied Pharmacy, 2013, 30(4): 360-364.
[15] ZHANG Weiping, WANG Jue, RAN Ran. Study on the mechanism of curcumin reversing TKI-targeted drug resistance in non-small cell lung cancer[J]. China Modern Physician, 2017, 55(25): 37-41, 169.
[16] Hou Z, Tong X, Peng Y, et al. Broad targeting of triptolide to resistance and sensitization for cancer therapy[J]. Biomedicine & Pharmacotherapy, 2018, 104: 771-780.
[17] BAI Liping, KANG Xiangpeng, LIN Li, et al. Experimental study of autophagy-mediated tretinoin to enhance the therapeutic effect of cetuximab on SW480 cells[J]. Chinese Pharmacology Bulletin, 2019, 35(3): 396-402.
[18] Zhang Y, Guo F. Analysis of the synergistic effect of tretinoin combined with gefitinib on EGFR-mutated NSCLC cells[J]. Chinese Pharmacy, 2023, 34(18): 2219-2225.
[19] Wu Jiahui. Mechanistic study on the reversal of gefitinib resistance in NSCLC by opsin H through Notch3 pathway [D]. Jiangxi University of Traditional Chinese Medicine, 2023.
[20] Li Guangda. Study on the mechanism of intervening drug resistance of human NSCLC by combining gefitinib with the additive formula of Guoben Abolishing Tumor Capsule [D]. Beijing University of Chinese Medicine, 2021.
[21] Ru Y, Chen X, Wang J, et al. Polysaccharides from Tetrastigma hemsleyanum Diels et Gilg: Extraction optimization, structural characterizations, antioxidant and antihyperlipidemic activities in hyperlipidemic mice[J]. International Journal of Biological Macromolecules, 2019, 125: 1033-1041.
[22] HE Jiaqi, LI Juanjuan, LU Xiaocai, et al. Reversal of drug resistance in gefitinib-resistant lung adenocarcinoma cells by total flavonoids of Trifolium pratense[J]. Chinese Clinical Pharmacology and Therapeutics, 2021, 26(4): 368-375.
[23] ZHANG Ting, LI Ang, SUN Jian. Effects of Nourishing Yin and Detoxifying Formula on phosphorylation of PC9/R signaling protein AKT and expression of PTEN in human lung adenocarcinoma drug-resistant cells[J]. Journal of Traditional Chinese Medicine, 2020, 48(1): 11-16.
[24] Zhang Jue. Study on the mechanism of acquired resistance to EGFR-TKIs in lung cancer by Yiqi and phlegm elimination formula [D]. Guangzhou: Guangzhou University of Traditional Chinese Medicine, 2021.
[25] KANG Xiaohong, GONG Yabin, WANG Lifang, et al. Effects and mechanism of toadstool combined with gefitinib on lung cancer cell H1975[J]. Chinese Journal of Integrative Medicine, 2013, 33(8): 1081-1085.
[26] YU Ya Ya, ZHU Yan Juan, XIAO Zhen Zhen, et al. Effects of Zhi Mu and Dried Ginger on Gefitinib Resistance in Non-Small Cell Lung Cancer Mediated by Abnormal Activation of PI3K/AKT Pathway and Mechanism[J]. New Chinese Medicines and Clinical Pharmacology, 2023, 34(11): 1525-1533.
[27] Maheswaran S, Sequist L V, Nagrath S, et al. Detection of Mutations in EGFR in Circulating Lung-Cancer Cells[J]. New England Journal of Medicine, 2008, 359(4): 366-377.
[28] LIU Hao, FANG Suping, ZHANG Xiaoxiao. Modulation of T790M and c-Met by Fuzheng detoxification formula improves acquired resistance to gefitinib[J]. World TCM, 2021, 16(8): 1221-1225.
[29] ZHANG Gao Chenxi, YANG Xinghui, SHU Qijin. In vitro study on the inhibition of gefitinib resistance caused by T790M mutation and c-MET amplification by aqueous extract of southern red bean curd[J]. Chinese Journal of Integrative Medicine, 2020, 40(6): 715-720.
[30] Zheng F. Molecular mechanism of berberine and its combination with gefitinib to inhibit NSCLC cell proliferation and EMT[D]. Guangzhou: Guangzhou University of Traditional Chinese Medicine, 2020.
[31] Tseng, Chao-Peng. Inhibition of gefitinib-resistant non-small cell lung cancer by cucurbitacin B [D]. Guangzhou: Southern Medical University, 2019.
[32] Nana Huang. Study on the correlation between TCM constitution, evidence type and adverse immune

response in advanced non-small cell lung cancer [D]. Dalian: Dalian Medical University, 2024.
[33] CHEN Weiwei. Analysis of the distribution of lung adenocarcinoma patterns and the use of traditional Chinese medicine [D]. Shenyang: Liaoning University of Traditional Chinese Medicine, 2023.
[34] Wang X-J, Zhou R-J, Zhang N, et al. 20(S)-ginsenoside Rg3 sensitizes human non-small cell lung cancer cells to icotinib through inhibition of autophagy[J]. European Journal of Pharmacology, 2019, 850: 141-149.
[35] MONG Jiaquan, JIAO Lijing, XU Ling. Recent clinical studies on Chinese medicine combination therapy for delaying resistance to EGFR-TKIs in non-small cell lung cancer[J]. Modern Journal of Integrative Medicine, 2022, 31(10): 1445-1449.
[36] JIANG Lifeng, SAN Feng, LIU Huaimin, et al. Clinical efficacy of Gefitinib-acquired resistance in non-small cell lung cancer treated with lung-cleansing, stasis-removing and detoxifying formula[J]. Chinese Journal of Traditional Chinese Medicine, 2023, 38(11): 5575-5578.