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REVIEW

Traditional Chinese Medicines as Anticancer Agents for Non-Small Cell Lung Cancer with EGFR Mutations: A Review

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Abstract: Non-small cell lung cancer (NSCLC) accounts for 85% of all cases of lung cancer cases. Epidermal growth factor receptor (EGFR) with L858R/T790M mutations are commonly found in clinical practice and usually results in resistance to first- and second-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs). Osimertinib is currently the first-line treatment choice for patients with EGFR L858R/T790M mutations, however, as to other EGFR-TKIs, resistance inevitably occurs. There is substantial evidence supporting the efficacy of traditional Chinese medicine (TCM) in the prevention and treatment of non-small cell lung cancer (NSCLC). The mechanisms underlying these effects involve the modulation of key cellular processes, including proliferation, apoptosis, cell cycle regulation, migration, invasion, autophagy, and epithelial–mesenchymal transition. TCM achieves these effects by regulating multiple signaling pathways and mechanisms, while also exhibiting synergistic interactions with EGFR tyrosine kinase inhibitors (TKIs). This review highlights the mechanisms through which TCM influences NSCLC patients harboring EGFR mutations, offering a promising therapeutic strategy for those with EGFR-TKI resistance.

Keywords: traditional Chinese medicine, NSCLC, EGFR, L858R/T790M mutations

Background

Lung cancer is the second most prevalent form of cancer worldwide, followed by breast cancer, however, it has the highest mortality rate among all malignant tumors.[1] A substantial proportion of patients are diagnosed at an advanced stage, with an estimated five-year survival rate of approximately 15%.[2] The oncogenic drivers of non-small cell lung cancer (NSCLC) include the epidermal growth factor receptor (EGFR), the anaplastic lymphoma kinase (ALK), the c-Ros oncogene 1 (ROS1), and the MET proto-oncogene. The most prevalent mutation type is an activating mutation in the tyrosine kinase domain of EGFR.[3]

The EGFR gene is located on the short arm of chromosome 7 (7p12-14) and consists of 28 exons. Exons 18 to 21 encode the tyrosine kinase (TK) domain, which represents the major hotspot for mutations in non-small cell lung cancer (NSCLC). These mutations typically affect tyrosine kinase activity and drug sensitivity. EGFR mutations can be broadly categorized into classical (sensitizing) mutations and resistance-associated mutations.

Classical sensitizing mutations refer to EGFR alterations that confer high sensitivity to tyrosine kinase inhibitors (TKIs), accounting for approximately 85–90% of all EGFR mutations. The two most common types are exon 19

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deletions (Ex19del) and the exon 21 point mutation L858R. Exon 19 deletions typically involve the removal of amino acid residues 746–750, while the L858R mutation results in the substitution of leucine with arginine at position 858. L858R substitution destabilizes the inactive conformation of the kinase domain, promoting constitutive activation. Both mutations disrupt the structure of the kinase domain: L858R occurs in the N-terminal portion of the activation loop's C-lobe, favoring an active conformation, while Ex19del precedes the αC-helix of the N-lobe, shortening the αC-loop and impairing the inactive conformation.[4] Clinically, patients harboring classical EGFR mutations respond significantly better to first-, second-, and third-generation TKIs compared to standard platinum-based chemotherapy. EGFR-targeted therapies have demonstrated clear benefits in terms of response rate, progression-free survival (PFS), and overall survival (OS).[5] Notably, patients with exon 19 deletions tend to have longer PFS than those with L858R mutations, which may be related to differences in downstream signaling activation, such as the PI3K/AKT pathway.[6,7]

Resistance-associated mutations include alterations such as T790M and C797S. The T790M mutation, often referred to as a "gatekeeper" mutation, occurs in exon 20 and contributes to resistance to first- and second-generation EGFR TKIs by creating steric hindrance and increasing the affinity of the kinase for ATP. Clinically, T790M is highly significant due to its high prevalence (50–70%) in EGFR-mutant lung adenocarcinomas that progress during treatment with first- or second-generation TKIs. Importantly, tumors harboring T790M remain sensitive to third-generation TKIs, such as osimertinib.[8,9] The EGFR C797S mutation is a common acquired resistance mechanism following treatment with third-generation EGFR-TKIs, such as osimertinib. This mutation substitutes cysteine at position 797 in the EGFR kinase domain with serine, preventing irreversible inhibitors (like osimertinib) from binding covalently to the ATP-binding site[10] The occurrence of this mutation, in relation to the T790M mutation (a second-generation resistance marker), significantly impacts the choice of subsequent treatment strategies, depending on whether the mutations are in cis or trans configuration. In the cis configuration, the C797S and T790M mutations are located on the same allele. This configuration renders EGFR kinase activity resistant to inhibition by any existing EGFR-TKI, either alone or in combination, because the drug cannot effectively bind to the mutation site.[11] Cis mutations account for over 80% of C797S mutation cases and represent the predominant form of resistance following third-generation TKI treatment. In the trans configuration, the C797S and T790M mutations are located on different alleles, and their spatial separation allows first-generation TKIs (such as gefitinib) to bind to the C797S-mutant allele, while third-generation TKIs (such as osimertinib) inhibit the T790M-mutant allele. This combination therapy can restore sensitivity.[12] However, trans mutations are relatively rare, accounting for less than 30% of C797S cases. Combination therapy with gefitinib (targeting the C797S-mutant allele) and osimertinib can significantly improve the objective response rate (ORR) in patients with trans mutations.[13,14]

The exon 19 deletion and the exon 21 L858R substitution are two of the most prevalent mutations.[15] The prevalence of EGFR mutations varies by country and location; for instance, the prevalence is significant higher in Asian women, particularly those who are nonsmokers, when compared to other populations.[16] Compared with exon 19 deletion, the L858R mutation has resulted in a conformational change in the tyrosine kinase domain of the EGFR, keeping it in a continuously active state, which reduces the tumor's responsiveness to EGFR-TKI medications. Therefore, the response to EGFR-TKIs is not as optimal as that observed with exon 19 deletion.[7] Secondary T790M mutations account for approximately 50–60% of acquired resistance to first- or second-generation EGFR TKIs.[17] The T790M mutation prevents first- or second-generation EGFR-TKIs from binding to the ATP-binding pocket of EGFR, blocking EGFR-TKI-mediated suppression of downstream signaling and potentially leading to disease progression.[18]

Due to these EGFR mutations in NSCLC, EGFR TKIs have emerged as a breakthrough therapeutic alternative for NSCLC patients and are becoming the primary treatment option.[19] For example, Osimertinib is a third-generation EGFR TKI that has shown excellent activity in controlling brain metastases, and several studies have shown[20] patients with EGFR-mutated NSCLC are more sensitive to EGFR-TKI therapy than conventional chemotherapy. The objective response rate (ORR) of patients with T790M mutation treated with first-line Osimertinib was significantly better (71% vs 31% $p<0.001$), however, the prevalence of grade 3 or higher adverse events was significantly lower than that in the chemotherapy group.[21] Acquired drug resistance inevitably occurs, making it difficult to maintain the treatment efficacy.[22] BLU-945, a fourth-generation TKI, has a higher selectivity and a better curative effect in patients with L858R/C797S/T790M mutations than in those with 19del/C797S/T790M mutations. Unfortunately, there is currently no standard treatment or approved drug for NSCLC patients with EGFR C797S mutation, so it is important to identify

adjuvant treatment options for those carrying L858R/T790M mutations through the mining of traditional Chinese medicines (TCMs), including Chinese herbs medicines (CHMs), to overcome the existing barriers related to the lack of treatment options.

TCMs have been used for millennia and offers numerous advantages, including multi-target and multi-pathway activity and a higher anti-tumor safety. A meta-analysis showed that CHM with EGFR TKIs can significantly delay acquired resistance while increasing the duration of ORR in patients treated with EGFR TKIs and reducing the incidence of adverse events.[23] The mPFS of patients receiving both EGFR TKIs and CHMs (13 months) was significantly longer than that of patients receiving EGFR TKIs alone (8.8 months). In the exon 19 deletion and L858R mutation subgroups, the mPFS increased by 2.5 months and 4.5 months in the combined group, respectively.[24] EGFR with T790M/L858R mutations in H1975, a human adenocarcinoma cell line, confer acquired EGFR-TKI resistance.[25] Recently, many studies have focused on H1975 cells, leading to an in-depth investigation of the mechanism of dual-target resistance. This review focuses on the mechanisms of TCMs in dual EGFR mutations (L858R/T790M), providing a basis for the development of new treatment options for patients with EGFR TKI treatment failure (Figure 1).

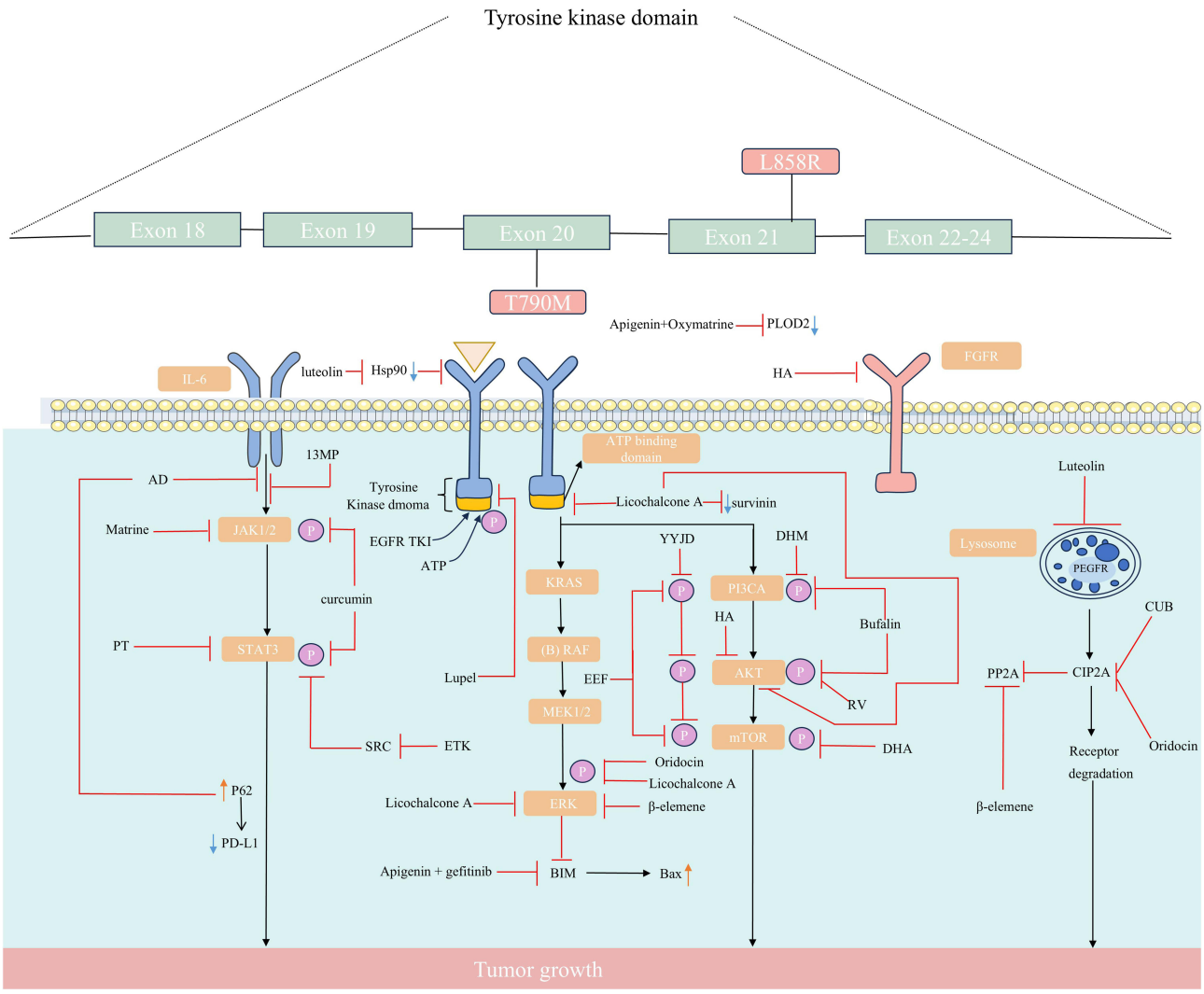

Figure 1 The active compounds of Traditional Chinese Medicines and the Chinese herb formula act on signaling pathways.

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Traditional Chinese Medicine Compounds

Jinfukang Oral Liquid

Huangqi is the main ingredient of Jinfukang Oral Liquid (JFK), a combination of 12 herbs, including Huangqi; previous research has clearly shown that JFK can mitigate the adverse effects of chemotherapy associated with NSCLC.[26] By inhibiting aerobic glycolysis, JFK may reduce the amount of adenosine triphosphate (ATP) and lactic acid produced. It also inhibits the function of three key enzymes in the glycolysis pathway, namely, hexokinase 2 (HK2), phosphofructokinase (PFKP), and pyruvate kinase muscle isozyme 2 (PKM2). According to in vivo research, gefitinib and JFK combined treatment lasting for 21 days dramatically suppressed the tumor growth rate of H1975 xenograft mice by 49.95% compared to the control group (Table 1 and Figure 2).

FuZhengKangAi

A study has shown that FuZhengKangAi (FZKA) significantly enhances the therapeutic efficacy of gefitinib and delays the emergence of gefitinib resistance in patients with lung adenocarcinoma (LUAD). FZKA exerts its effects by targeting and suppressing the promoter activity of EZH2, thereby inhibiting the phosphorylation of ERK1/2 and the expression of its downstream transcription factor Snail. This process reverses epithelial-mesenchymal transition (EMT) and reduces EGFR protein levels, ultimately restoring the sensitivity of gefitinib-resistant H1975 cells (harboring EGFR L858R/T790M mutations) to gefitinib and synergistically suppressing tumor growth. However, data about tumor suppression rates are currently unavailable, further investigation is required more accurately to assess the inhibitory impact of these drugs on tumors.[29]

Table 1 Effects of Decoction on H1975 Cells

Formula	Herb	Primary Mechanism	Effects	In vivo Model
Yang-Yin-Jie-Du (YYJDD)[27]	Beishashen (Glehniae Radix), Mai Dong (Ophiopogon japonicus (L. f). Ker Gawl).), Bai He (Lilium brownii var. viridulum Baker), Shi Hu (Dendrobium nobile Lindl.), Baihuasheshecao (Scleromitrion diffusum (Willd). R. J. Wang), Nanfanghongdoushan (Taxus wallichiana var. mairei (Lemee & H. Léveillé) L. K. Fu & Nan Li), Chen Pi (Citrus reticulata Blanco), Dang Shen (Radix Codonopsis Pilosulae)	Downregulation of the PI3K/AKT pathway	↑Apoptosis	H1975 xenograft mouse model
Huanglian Jiedu Decoction (HJD)[28]	Zhi Zi (Fructus gardenia), Huang Bai (Cortex phellodendri), Huang Qin (Radix scutellariae), Huang Lian (rhizoma coptidis)	Regulation of the STAT3/Bcl-2 signalling pathway	↑Apoptosis	H1975 xenograft mouse model
FuZhengKangAi (FZKA)[29]	Tai Zi Shen (Pseudostellaria Heterophylla (Miq).), Huang QiPseudostellaria Heterophylla (Miq.), Yi Yi Ren (Yi Yi Ren), Shancigu (Gremastra Appendiculata (D.Don) makino), Baihuasheshecao (Hedyotis Diffusa Willd), Long Kui (Solanum Nigrum L.), Shi Jian Chuan (Salvia Chinensis Benth.), Bayuezha (Bayuezha), Shepaole (Shepaole), Bai Zhu (Atractylodes Macrocephala Koidz.), Ezhu (Curcuma Phaeocaulis Val.), Gan Cao (Glycyrrhiza Uralensis Fisch)	Regulation of the EZH2/Snail/EGFR pathway	↑Apoptosis	H1975 xenograft mouse model
JieBeiHeJi (JB)[30]	Jei Geng (Platycodon grandiflorus (Jacq). A. DC.), Zhe Beimu (Fritillaria thunbergii Miq.), Ku Xingren (Semen Armeniacae Amarum.), Mai Dong (Ophiopogon japonicus (L. f). Ker Gawl).), Huang Qin (Scutellaria baicalensis Georgi), Pi Paye (Eriobotrya japonica Thunb.), GanCao (Glycyrrhiza uralensis Fisch).	Blockade of the PI3K/AKT MAPK pathway	↑Apoptosis	/
Shenqi Fuzheng injection (SFI)[31]	Dang Shen (Radix Codonopsis Pilosulae), Huang Qi (Astragalus membranaceus (Fisch).)	Regulation of the MAPK/SREBP1	↑Apoptosis	H1975 xenograft mouse model

Abbreviations: SREBP1, Sterol regulatory element-binding protein 1; mTOR, mammalian target of rapamycin; MAPK, Mitogen-activated protein kinase; PI3K, Phosphatidylinositide 3-kinase; AKT, Protein kinase B; STAT3, Signal transducer and activator of transcription 3; Bcl-2, B-cell lymphoma 2; EZH2, Enhancer of zeste homolog.

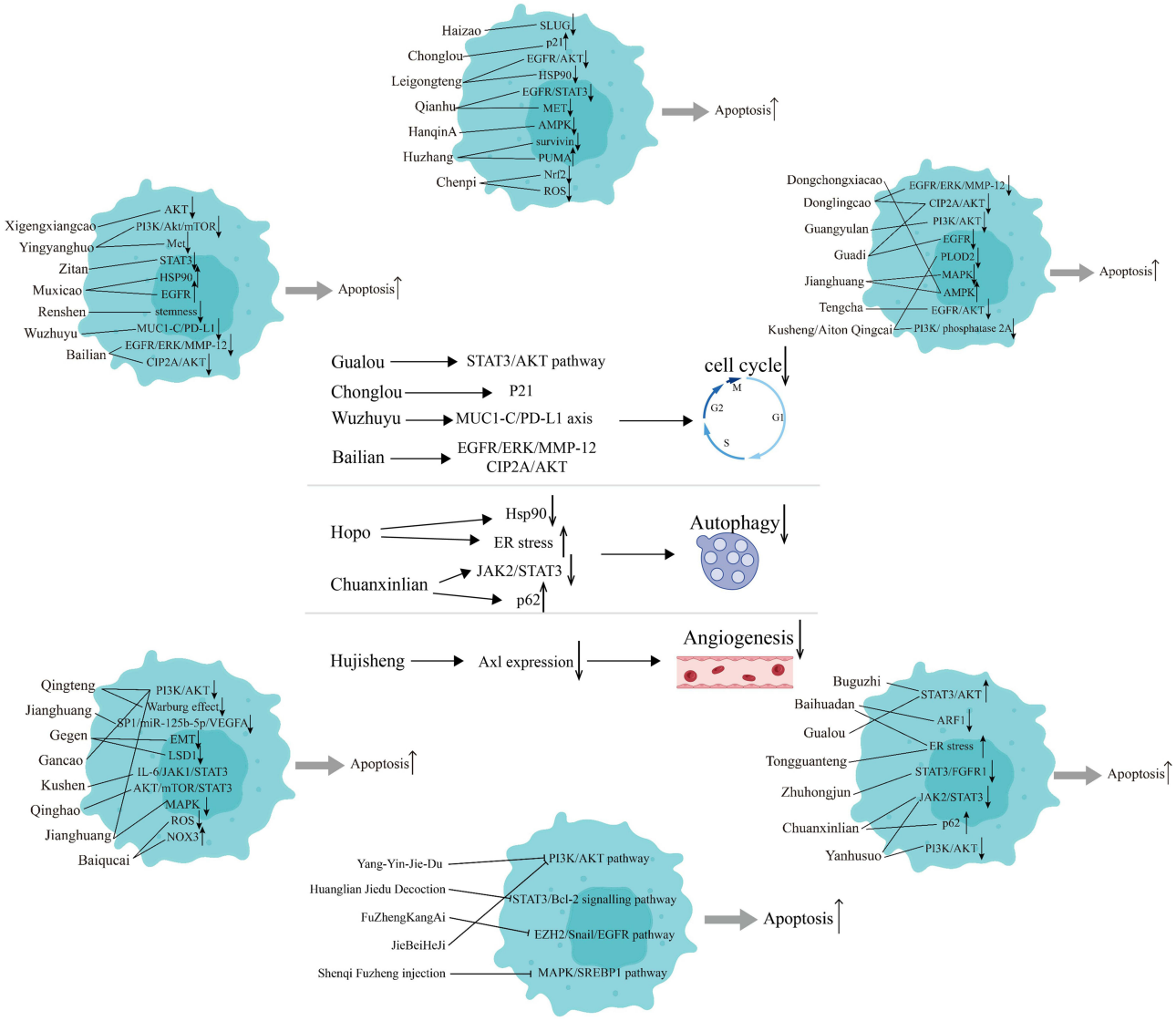

Figure 2 Summary of the mechanisms by which Traditional Chinese Medicine compounds and monomers act on H1975 cells.

JieBeiHeJi

JieBeiHeJi (JB) enhances the cytotoxic effect of gefitinib against EGFR T790M-mutant resistant NSCLC cells (H1975) by blocking the mitochondrial translocation of Bcl-2, thereby inducing mitochondrial apoptosis. In addition, JB inhibits the PI3K/AKT and MAPK signaling pathways, reversing drug resistance mediated by apoptosis evasion and downstream pathway activation.[30]

HuanglianJiedu

Huanglian Jiedu (HJD) was initially referenced in Wang Tao's Wai-tai-mi-yao (Arcane Essentials from the Imperial Library), a Tang period text that is frequently cited in medical literature.[32] In EGFR-TKI-resistant cells, HJD restores sensitivity to erlotinib-induced apoptosis by inhibiting STAT3 phosphorylation (specifically blocking activation at the Tyr705 site) and downregulating the expression of anti-apoptotic proteins Bcl-2 and Bcl-XL. This relieves the inhibition of the mitochondrial apoptotic pathway and disrupts the STAT3/Bcl-2 signaling cascade, thereby promoting apoptosis.[28]

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Feiyanning Prescription

The Feiyanning formula (FYN) has been employed in the clinical setting for over two decades and has been demonstrated to bring benefits in prolonging patients' lifespan and improving the quality of life (QoL), while it showed a minimal toxicity and adverse effects in previous studies.[33] The proliferation of H1975 cells was found to be dose-dependently inhibited by FYN in vitro. The combination of FYN and gefitinib exhibited markedly greater efficacy in impeding the growth of H1975 cells.

Shenqi Fuzheng Injection

Shenqi Fuzheng injection (SFI) is derived from aqueous extracts of two traditional Chinese Medicinal herbs, Codonopsis pilosula and Astragalus membranaceus. Both of these herbs are known for their ability to invigorate Qi.[34] Clinical studies have indicated that the combination of SFI with first-generation EGFR-TKIs is highly beneficial with the potential to prolong PFS and alleviate adverse events in patients with EGFR-mutated lung cancers.[35] SFI targets lipid metabolism by blocking the MAPK/SREBP1 pathway, thereby inhibiting SREBP1-mediated fatty acid and cholesterol synthesis. This weakens the lipid-dependent survival of tumor cells, enhances the binding efficiency of EGFR-TKIs to mutant receptors, and directly induces apoptosis in resistant cells through activation of the Bcl-2/Caspase pathway.[31]

Traditional Chinese Medicine Monomers

Flavonoids

Apigenin

The primary plant source of apigenin (4′,5,7-trihydroxyflavone) is Herba Artemisiae Annuae,[36] this bioflavonoid compound has been found to inhibit the tumor cell cycle, cause cell death, and boost the immune system.[37–39] Apigenin has the potential to promote the function of antitumor immunity and improve the efficacy of anticancer therapies by upregulating the expression of programmed cell death-ligand 1 (PD-L1).[40] The coadministration of gefitinib and apigenin resulted in a reduction in the levels of Gluts and Malignant T-cell amplified sequence 1 (MCT-1), thereby interfering with three distinct oncogenic drivers such as cancer-Myc (c-Myc), Hypoxia-inducible factor-1 (HIF-1) and EGFR. Furthermore, apigenin has the capacity to inactivate the mitogen-activated protein kinase (AMPK) signaling pathway and downregulate glucose metabolism. Consequently, this process effectively targets the energy metabolism of H1975 cells, leading to aberrant energy metabolism and ultimately promoting cell apoptosis (Table 2 and Figure 2).[41]

Tangerine

The effects of Chenpi include the regulation of Qi, the fortification of the spleen, and the resolution of phlegm through the process of "drying dampness". Tangerine (TG), an extract derived from Chenpi, overcomes drug resistance by targeting the key oxidative stress regulator Nrf2, thereby weakening the cancer cells' defense against oxidative stress. It synergizes with osimertinib to enhance apoptotic sensitivity in EGFR-TKI–resistant lung cancer cells.[64]

Epimedium Koreanum Nakai

Epimedium is a well-known herbal remedy with a history of use spanning over 2000 years, and it is widely used as a tonic and aphrodisiac. The combination of E. koreanum Nakai (EEF) with gefitinib is observed to effectively inhibit the growth of H1975 cells via the EGFR/AKT/mTOR pathway. The combination of gefitinib and EEF demonstrates superior tumor growth inhibition in H1975 xenograft models compared to gefitinib alone or control treatment, highlighting its potential therapeutic value. Further investigation is needed to evaluate its safety in humans.[66]

Flavokavin B

Flavokavin B (FKB) is a novel flavonoid isolated from kava root extract, which has impressive antitumor properties against malignancies such as breast, colon and gastric cancer.[82,83] FKB suppresses the growth and migration of H1975 tumor cell by upregulating epithelial cadherin (E-cadherin), stimulating the degradation of EGFR, and downregulating matrix metallopeptidase 9 (MMP-9) and vimentin.

Table 2 Effects of Natural Product on H1975 Cells

Ingredient	Herb Source	Primary Mechanism	Effects	In vivo Model
Psorachromene[42]	Buguzhi (Psoralea corylifolia Linn).	Inhibits the STAT3/AKT pathway	↑Apoptosis	H1975-MS35 H1975 Mice (in H1975 cell in vitro)
Plumbagin[43]	Baihuadan (Plumbago zeylanica L)	Increases CD8+ T cell infiltration, suppresses ARF1 expression, stimulates ER stress	↑Apoptosis	H1975 xenograft mouse model
Trichosanthes kirilowii[44]	Gualou (Trichosanthes Kirilowii Maxim)	Inhibits the STAT3/AKT pathway	↑Apoptosis↓Cell cycle	/
Marsdenia tenacissima extract[45]	Tongguanteng (Marsdenia tenacissima (Roxb). Wight et Arn).	Induces ER stress	↑Apoptosis	H1975 xenograft mouse model
Liposomal honokiol[46]	Hopo (Magnolia officinalis Rehd.etWils).	Stimulates Hsp90 client proteins degradation Induces ER stress	↑Autophagy	/
Hypocrellin A[47]	Zhuhongjun (Hypocrella bambusea)	Inhibits STAT3/FGFR1 pathway	↑Apoptosis	H1975 xenograft mouse model
Andrographolide[48]	Chuanxinlian (Andrographis Herba)	Inhibition of JAK2/STAT3 Upregulation of p62	↑Apoptosis Autophagy	H1975 xenograft mouse model
13-methyl-palmatrubine[49]	Yanhusuo (Corydalis Rhizoma)	Inhibition of JAK2/STAT3 PI3K/AKT pathway Shifts tumor macrophages from M2 to M1	↑Apoptosis	/
Oridonin[50]	Donglingcao (Rabdosia rubescens (Hemsl).)	Inhibits EGFR/ERK/MMP-12 and CIP2A/Akt signalling pathways	↑Apoptosis	H1975 xenograft mouse model
Methanol-ethyl acetate of Magnolia grandiflora[51]	Guangyulan (Magnolia grandiflora linn)	Inhibits PI3K/AKT	↑Apoptosis	H1975 xenograft mouse model
Cucurbitacin B[52]	Guadi (Calyx Cucumis)	Inhibits the CIP2A/PP2A/Akt signaling Axis Stimulates EGFR degradation	↑Apoptosis	H1975 xenograft mouse model
Apigenin Oxymatrine[53,54]	Kusheng (Sophora flavescens) Aiton Qingcai (Apium graveolens)	Inhibits PI3K/protein phosphatase 2A Downregulate s PLOD2	↑Apoptosis	/
β-elemene[55]	Jianghuang (Curcuma longa)	Inhibits MAPK activity Stimulates AMPKα activity	↑Apoptosis	/
Dihydromyricetin[56]	Tengcha (Ampelopsis grossedentata (Hand. - Mazz). W. T. Wang)	Inhibits the EGFR/Akt/survivin pathway	↑Apoptosis	H1975 xenograft mouse model
Cordycepin[57]	Dongchongxaicao (Ophiocordyceps sinensis)	Activates the AMPK pathway	↑Apoptosis	H1975 xenograft mouse model
Fucoidan[58]	Haizao (Sargassum)	Downregulates slug	↑Apoptosis	H1975 xenograft mouse model
Polyphyllin[59,60]	Chonglou (Paridis rhizoma).	Elevates P21 expression	↓ Cell cycle	H1975 xenograft mouse model
Celastrol[61]	Leigongteng (Tripterygium wilfordii)	Inhibits the EGFR/Akt pathway Suppresses Hsp90 client protein expression	↑Apoptosis	/
Extract of Peucedanum praeruptorum[62]	Qianhu (Peucedanum praeruptorum Dunn)	Inhibits the EGFR/STAT3 pathway Inhibits MET activity	↑Apoptosis	H1975 xenograft mouse model

(*Continued*)

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Table 2 (Continued).

Ingredient	Herb Source	Primary Mechanism	Effects	In vivo Model
Apigenin[41]	HanqinA(Apium graveolens L).	Inhibition of the glucose metabolism and the AMPK pathway	↑Apoptosis	/
Resveratrol[63]	Huzhang (Reynoutria japonica Houtt).	Downregulates survivin Up regulates PUMA	↑Apoptosis	/
Tangerine[64]	Chenpi (Citrus Reticulata)	Downregulates Nrf2 Downregulates ROS	↑Apoptosis	/
Lysimachia capillipes capilliposide[65]	Xigengxiangcao (Lysimachia capillipes)	Inhibits AKT activation and restores gefitinib sensitivity	↑Apoptosis	PC-9-GR xenograft mouse model (in H1975, PC-9-GR in vitro)
Epimedium koreanum Nakai[66]	Yingyanghuo (Epimedium brevicornu Maxim).	Inhibits of the PI3K/Akt/mTOR pathway Inhibits Met expression	↑Apoptotic	PC-9/GR H1975 xenograft mouse model (in PC-9/GR, H1975 cell in vitro)
Pterostilbene[67]	Zitan (Pterocarpus santalinus)	Abrogates the STAT3 pathway	↑Apoptosis	/
Luteolin[68]	Muxicao (Reseda odorata L).	Inhibits Hsp90 EGFR degradation	↑Apoptosis	H1975 xenograft mouse model
Ginsenoside Rg3[69]	Renshen (Panax Ginseng C. A. Mey).	Reduces the stemness of NSCLC	↑Apoptosis	H1975 xenograft mouse model
Evodiamine[70]	Wuzhuyu (Evodiae Fructus)	Inhibits the MUC1-C/PD-L1 axis Promotes CD8+ T cell infiltration	↓ Cell cycle	H197 xenograft 5Mice
Lupeol[71]	Bailian (Ampelopsis Japonica)	Inhibits the EGFR/ERK/MMP-12 CIP2A/Akt pathway	↑Apoptosis ↓Cell cycle	/
Sinomenine[72]	Qingteng (Menispermum acutum Thunb).	Suppresses the Warburg effect and PI3K/AKT signalling	↑Apoptosis	/
Betulinic acid[73]	Suanzaoren (Ziziphi Spinosae Semen)	Arrests the cell cycle by regulating related proteins	↑Apoptosis Autophagy ↓Cell cycle	/
Curcumol[74]	Jianghuang (Curcuma longa L).	Regulates the SP1/miR-125b-5p/VEGFA axis	↑Apoptosis	/
Puerariae Lobatae Radix[75]	Gegen (Radix Puerariae)	Inhibits EMT and LSD1 expression	↑Apoptosis	/
LicoChalcone A[76]	Gancao (Licorice)	Inhibits the survivin PI3K/AKT pathway	↑Apoptosis	H1975 xenograft mouse model
Matrine[77]	Kushen (Sophorae Flavescentis Radix)	Inhibits the IL-6/JAK1/STAT3 pathway	↑Apoptosis	H1975 xenograft mouse model
Artemisinin[78]	Qinghao (Artemisia Annua L).	Inhibits the AKT/mTOR/STAT3 pathway	↑Apoptosis	/
Curcumin[79]	Jianghuang (Curcuma longa)	Inhibits the MAPK and PI3K/AKT pathways	↑Apoptosis	
Sanguinarine[80]	Baiqucai (Chelidonii Herba)	Increases ROS level Upregulate NOX3	↑Apoptosis	/
Visucm album extract[81]	Hujisheng (Viscum coloratum (Kom). Nakai)	Suppresses Axl expression	↓Angiogenesis	/

Abbreviations: STAT3, signal transducer and activator of transcription 3; AKT, protein kinase B; ARF1, endoplasmic reticulum stress; Hsp90, heat shock protein 90; FGFR1, fibroblast growth factor receptor 1; JAK, Janus kinase; PI3K, phosphatidylinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; CIP2A, cancer inhibitor of protein phosphatase 2A; PP2A, protein phosphatase 2A; AKT, protein kinase B; EGFR, epidermal growth factor receptor; AMPK, mitogen-activated protein kinase; PUMA, p53 upregulated modulator of apoptosis; c-Met, cellular-mesenchymal epithelial transition factor; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; NSCLC, non-small cell lung cancer; MUC1-C, MUC1 C-terminal domain; PD-L1, programmed cell death-Ligand 1; CD, cluster of differentiation; SP1, transcription factor Sp1; VEGFA, vascular endothelial growth factor A; EMT, mesenchymal transition; LSD1, lysine-specific histone demethylase 1A; NOX3, nicotinamide adenine dinucleotide phosphate oxidase 3; MET, cellular-mesenchymal epithelial transition factor.

Licochalcone A

Licochalcone A is derived from liquorice root and is widely used in the clinic, which has a broad spectrum of tumor-specific inhibitory effects on cancers.[84–86] It can overcome acquired resistance to gefitinib in NSCLC HCC827- gefitinib-resistant (GR) and PC-9-GR cells by inducing cellular-mesenchymal epithelial transition factor (c-Met) ubiquitination and inhibiting c-Met signaling.[87] Licochalcone A has been shown to bind to the ATP-binding domain of EGFR, which can further reduce the expression of the EGFR downstream kinases such as ERK1/2 and Akt and decrease the expression of survivin, thereby increasing the responsiveness to targeted therapies.[76]

Viscum Album Extract

Viscum album is a semi-parasitic plant that grows on a host tree of the genus Fraxinus[88] and has a potent pharmaceutical effect. Viscum album extract (VAE) targets Axl, a receptor tyrosine kinase that regulates cell growth, survival, proliferation, invasion, migration and angiogenesis, and it is overexpressed in many malignancies.[89] VAE also successively increases p21 protein levels, leading to cell cycle arrest, and decreases X-linked inhibitor of apoptosis protein (XIAP) levels and then contributing to apoptosis.[81]

Luteolin

The flavonoid luteolin is found mainly in honeysuckle, wild chrysanthemum and whole-leaf green orchids.[90] Luteolin inhibits the association of heat shock protein 90 (Hsp90) with mutant EGFR receptors by blocking the pathway of PI3K/Akt/mTOR signaling, which results in the suppression of NSCLC progression.[68] Therefore, the ability of luteolin to block both EGFR and Hsp90 suggests its utility as an adjuvant drug to enhance the effect of the current treatment regimens in patients with dual EGFR T790M/L858R mutations.

Dihydromyricetin

Dihydromyricetin (DHM) is a natural derivative of the woody vine Vitis vinifera.[91] It possesses pharmacological properties such as anti-inflammatory and antibacterial effects.[92] DHM significantly reduces the viability of H1975 cells by disrupting the EGFR-Akt signaling pathway, leading to decreased activation of AKT and ERK1/2, degradation of survivin, and induction of apoptosis.[56]

Puerariae Lobatae Radix

Puerariae Lobatae Radix is a component of a commonly used clinical drug - Gegen, which relieves muscle pain, reduces fever, and treats measles. Gegen has been shown to exert positive effects in various cancers in previous studies.[93–95] DHM significantly reduces the viability of H1975 cells by disrupting the EGFR-Akt signaling pathway, leading to decreased activation of AKT and ERK1/2, degradation of survivin, and induction of apoptosis.[75]

Lysimachia Capillipes Capilliposide

The plant *Lysimachia capillipes (LC) Hemsl*, which is native to south-eastern China, has been used extensively to treat coughs, menstrual disorders, rheumatism, and cancers. LC capilliposide can render radioresistant lung cancer cells more sensitive to radiation by activating the ERBB receptor feedback inhibitor 1 (ERRFI1)/EGFR/STAT3 signaling pathway.[96] There was no significant inhibition of cell growth after treatment with LC capilliposide alone for 72 hours. However, the addition of LC capilliposide can enhance the inhibitory effects of gefitinib, resulting in a decrease in the IC_{50}. Unfortunately, the mechanism is not yet known to decrease the cytotoxic effect. What's more, the related study did not investigate the underlying mechanism. However, an experiment using PC-9-GR cells harboring an EGFR T790M mutation showed that LC decreased the phosphorylation of AKT, a downstream EGFR signaling protein, and then induce apoptosis and overcome drug resistance in NSCLC.[65]

Phenol

Resveratrol

Resveratrol (RV), a naturally occurring polyphenol compound derived from the roots of white hellebore (Veratrum grandiflorum),[97] exhibits a promising potential as an anti-tumor agent due to its ability to activate sirtuin 1 (SIRT1) and inhibit the downstream EGFR pathway.[98] When combined with RV, erlotinib can significantly reduce the viability of

H1975 cells and induce them to apoptosis by producing more reactive oxygen species (ROS), decreasing P53 upregulated modulator of apoptosis (PUMA) levels, and downregulating antiapoptotic proteins, including survivin and the myeloid cell leukemia sequence 1 gene (Mcl-1). In addition, RV inhibits the AKT/mTOR/S6 pathway, which works in concert with erlotinib to enhance its anti-cancer activity in NSCLC cells. This is demonstrated by the reduction of p-AKT, p-mTOR, and p-S6K levels.[63]

Curcumin

Curcumin, an organic polyphenol found in turmeric, has anti-viral, anti-bacterial, antioxidant, anti-inflammatory, and anti-proliferative properties. The combination of curcumin and gefitinib exhibits enhanced anti-tumor effects against NCI-H1975 cells by more effectively inhibiting cell proliferation and colony formation, while promoting apoptosis. Curcumin also suppresses the activation of key signaling pathways, including p38, ERK1/2, and AKT, and enhances the pro-apoptotic activity of gefitinib.[99] Curcumin exerts its therapeutic effects against NSCLC by inhibiting angiogenesis and targeting the STAT3 signaling pathway through the downregulation of CD31, CD105, and the phosphorylation of STAT3 and JAK.[79]

Honokiol

Honokiol (HNK), a compound found naturally in the magnolia tree, has shown promise as an antitumor agent.[100] The combination of HNK and osimertinib reduced the levels of uncleaved poly (ADP-ribose) polymerase (PARP) when compared to either treatment alone, leading to apoptosis in osimertinib-resistant cells. In addition, co-treatment with HNK and osimertinib increased the abundance of the BCL2L11 gene (BIM) in drug-resistant cell lines; BIM plays an extremely important role in the sensitivity to osimertinib in NSCLC; this combination also decreased the expression of the myeloid cell leukemia sequence 1 gene (Mcl-1) and the p-ERK1/2 and p-ERK ratios.[101,102] In vivo, the concomitant use of HNK and osimertinib may inhibit tumor growth while having minimal impact on body weight in mice.[100] The co-administration of HNK and osimertinib significantly reduced the survival, colony formation, and proliferation of drug-resistant NSCLC cells with EGFR mutations, suggesting that HNK can neutralize osimertinib-resistant cells.

Liposomal Honokiol

Honokiol, which is isolated from Magnolia officinalis, is a commonly used herb in the clinic and can dry dampness to relieve mucus.[103] By increasing heat shock protein 90 (HSP90) acetyl levels and downregulating the EGFR signaling cascade effectors Akt and ERK1/2, lysosomal honokiol (LHK) promotes HSP90 client protein (HCP) degradation, and the effects mentioned above contribute to the autophagy of H1975 cells. Furthermore, in a xenograft model with subcutaneously implanted H1975 cells, LHK significantly reduced tumor growth in a dose-dependent manner. Notably, there were no pathogenic consequences or gross body weight loss in the key organ systems.[46]

Pterostilbene

Pterostilbene (PT), known as trans-3,5-dimethoxy-4'-hydroxystilbene, is a dimethyl ether analogue of resveratrol that has similar pharmacological properties but more advanced pharmacokinetic characteristics, such as increased lipophilicity, greater oral absorption, and a longer half-life.[104] PT enhances the therapeutic effect of osimertinib in NSCLC by inhibiting the activation of STAT3, YAP1, and CDCP1, key proteins involved in drug resistance. The combination of osimertinib and PT demonstrates a synergistic effect, offering potential benefits in extending progression-free survival (PFS) and delaying resistance development in NSCLC cells with L858R and T790M mutations.[67]

Glycoside

Fucoidan

Fucoidan is a TCM Kunbu extract that softens, firms, and disperses masses. Combination with fucoidan increases the sensitivity of H1975 cells to gefitinib by abolishing the transforming growth factor beta (TGFβR)/Slug axis and reversing EMT, as evidenced by the downregulated expression of Neural-cadherin (N-cadherin) and Twist. Additionally, Slug, a key EMT regulator that enhances the apoptotic pathway and increases the inhibitory effect of gefitinib, is downregulated. Furthermore, the combination index of fucoidan and gefitinib reached a value of 0.55, indicating a synergistic effect.[58]

Polyphyllin

Chonglou, an anti-tumor drug, has been used for thousands of years for heat-clearing and detoxification. The anti-tumor effect of chonglou is mainly attributed to its polyphyllin.[105] Polyphyllin II (PPII) and polyphyllin I (PPI) inhibit cell proliferation in a dose-dependent manner. According to earlier studies, high expression of P21 is a prerequisite for the responsiveness of NSCLC cells to gefitinib.[106] Polyphyllin VII (PPVII) enhances the efficacy of gefitinib by promoting cell cycle arrest and increasing P21 expression. It also inhibits the PI3K/AKT pathway, induces apoptosis, and helps reverse resistance to osimertinib in resistant NSCLC cells.[59] Without changing the body weight of the mice, the combination of Osimertinib and PPI significantly inhibited tumor growth.[60]

Ginsenoside Rg3

Ginseng is a widely used TCM with a long history. Ginsenoside Rg3 is the main pharmacological component of ginseng and can improve immune function, it also decrease tumor angiogenesis and aberrant inflammatory factor expression.[107] Therefore, it is frequently utilized in adjuvant therapy for various malignancies.[108–110] A previous study suggested that the ginsenoside Rg3 can boost the anti-cancer activity of gefitinib and induce the apoptosis of gefitinib-resistant cells.[111] Ginsenoside attenuates H1975 cell stemness and Osimertinib resistance by activating the Hippo signaling pathway. H1975-OR cells treated with the combined therapy had significantly reduced viability. An in vivo study also demonstrated that ginsenoside Rg3 can slow the growth of tumors.[69]

Cordycepin

A rare Chinese herbal remedy with good tonic properties is Dong-Chong-Xia-Cao. The active component derived from Dong-Chong-Xia-Cao has the chemical formula $C_{10}H_{13}N_5O_3$ and is known as cordycepin (CD).[112] Previous studies have revealed that CD can cause deep irreparable damage to DNA, promote PI3K/Akt phosphorylation and increase the production of reactive oxygen to induce cancer cell death.[113,114] As a tonifying TCM, CD may interfere with the progression of NSCLC without damaging normal lung cells. Moreover, by binding with AMPK, CD has a stronger killing effect on H1975 cells than on PC9 cells. At the concentrations of 50 mg/kg and 75 mg/kg, CD can significantly decrease tumor volume, however, it decreases slight weight loss in vivo.[57]

Terpenoid

β-Elemene

β-Elemene, which is extracted from *Curcuma Rhizoma*, exhibits a broad-spectrum antitumor effects, including the induction of tumor cell apoptosis, inhibition of tumor cell migration and tumor angiogenesis in H1975 cells.[115] β-Elemene can prevent the proliferation of lung cancer cells by inhibiting M2 macrophage polarization.[116] β-Elemene enhances the anti-tumor effects of erlotinib by inhibiting cancer cell invasion and migration, promoting apoptosis, and modulating key signaling pathways. Mechanistically, it activates AMPK signaling while downregulating the phosphorylation of mTOR, EGFR, and ERK, thereby inhibiting MAPK pathway activity.[55]

Triptolide

Triptolide (TPL) is an ancient Chinese medical preparation that has been used for the treatment of lupus erythematosus, rheumatoid arthritis, and nephritis. Triptolide (TPL) enhances the efficacy of EGFR-TKIs in NSCLC by promoting apoptosis through modulation of Bcl-2 and Bax expression. Additionally, molecular docking suggests that TPL interacts directly with mutant EGFR (T790M/L858R), potentially contributing to its synergistic anti-tumor effects.[117]

Betulinic Acid

Betulinic acid (BetA), a pentacyclic triterpene of the lupine type, is extracted primarily from birch trees. It is a phytochemical molecule that has been demonstrated to possess excellent anticancer potential, exhibiting strong cytotoxicity towards melanoma cells.[118] The combination of BetA and an EGFR-TKI, such as gefitinib or erlotinib, has been found to exert a greater inhibitive effect on H1975 cells than either treatment alone, leading to the increase of the ratio of Bax/Bcl-2, which provides evidence that apoptosis was triggered by the combination therapy. Furthermore,

the levels of the thymidylate synthases cell division protein kinase 6 (CDK6) and P62, which are cell cycle-related proteins and autophagy-related proteins, were found to decrease.[73]

Artemisinin

Derived from the annual Compositae family member Artemisia annua L, artemisinin has been used as a drug for more than 2000 years and saved numerous lives of malaria patients.[119] By blocking the nuclear factor kappa-B (NF-κB) signaling pathway, cellular glucose metabolism, and the canonical Wnt/β-catenin (Wnt/β-catenin) pathway, dihydroartemisinin (DHA) has been demonstrated to reduce cell proliferation, migration, invasion, cancer stem cells, and epithelial-to-mesenchymal transition (EMT) in NSCLC.[120,121] The combination of DHA and gefitinib has been observed to result in the phosphorylation of the Akt/mTOR/STAT3 pathway, which in turn leads to cell cycle arrest in the G2/M phase and an increase in the apoptosis rate to approximately 30%. This is significantly higher rate than that observed in cells treated with gefitinib alone, which exhibited an apoptosis rate of only 20%. Furthermore, the viability of cells treated with either DHA or gefitinib alone was significantly lower than that of cells treated by the combination of 10 μM gefitinib and 10 μM DHA. Consequently, a prospective therapeutic strategy that may circumvent resistance to TKI therapy for NSCLC may entail the combination of DHA and gefitinib.[78]

Curcumol

Curcumol represents a monomeric component of the TCM turmeric. Curcumol inhibits the proliferation of EGFR-TKI–resistant H1975 cells, with its anti-resistance effects linked to the modulation of transcription factor Sp1, miR-125b-5p, and VEGFA expression.[74,122]

Cucurbitacin B

Cucurbitacin B (CuB), the most prevalent member of the cucurbitacin family, has been demonstrated to induce apoptosis, reduce cell viability, and inhibit invasion in H1975 cells in a dose- and time-dependent manner. Cucurbitacin B (CuB) enhances the antitumor effect in EGFR-TKI–resistant NSCLC by downregulating the CIP2A/PP2A/AKT signaling axis, promoting EGFR degradation in lysosomes. CIP2A overexpression is associated with tumor progression, therapy resistance, and poor prognosis.[123] Cucurbitacin B (CuB) induces tumor cell apoptosis in NSCLC by inhibiting the CIP2A/PP2A signaling axis and suppressing the phosphorylation of ERK and Akt.[52]

Lupeol

Lupeol is a triterpenoid widely found in a variety of Chinese herbal medicines and food-derived plants. The MTT assays revealed that, following the administration of erlotinib or lupeol for a period of 72 hours in H1975 cells, lupeol exhibited a more pronounced inhibitory effect on H1975 cell activity than erlotinib. Lupeol has been proved to inhibit colony formation and cell proliferation while simultaneously triggering apoptosis in a dose-dependent manner, which is achieved by suppressing downstream signaling and the phosphorylation of the transcription activator STAT3. This is achieved by direct interaction with the tyrosine kinase domain of EGFR, which in turn reduces the expression of target genes such as cyclin D1 and survivin.[71]

Oridonin

In Chinese, the term "Donglingcao" refers to oridonin (Ori, $C_{20}H_{28}O_6$), a diterpenoid of the kaurene type that was first discovered in Rabdosia rubescens[135]. Ori disrupts the antitumor protein phosphatase 2A/protein phosphatase 2A/AKT (CIP2A/PP2A/AKT) and EGFR/ERK/matrix metalloproteinase-12 (MMP-12) signaling pathways, thereby preventing H1975 cells from proliferating, invading, and migrating. Oridonin has been proved to stimulate the activity of the tumor suppressor PP2A[124] and inactivate mitogen-activated extracellular signal-regulated kinase (MEK1) and ERK, thereby inhibiting the PI3K/Akt pathway.[50]

Andrographolide

Andrographolide (AD), derived from Andrographis paniculate, is a diterpene lactone compound, which has been demonstrated to induce tumor cell apoptosis, cell migration and invasion, what's more, it inhibits tumor angiogenesis and tumor cell cycle progression.[125–128] AD displays a dose-dependent inhibition of H1975 cell proliferation and

viability. In addition, molecular docking calculations showed that AD can bind to STAT3 with high affinity. This combination inhibits STAT3 phosphorylation and promotes ROS production, which further induces P62 accumulation and decreases PD-L1 levels, increasing the accumulation of P62-mediated selective autophagy in cells. Furthermore, an in vivo study demonstrated that AD inhibits the growth of tumor in H1975 tumor xenografts and prolongs survival in a Lewis lung carcinoma model while having minimal impact on mouse body weight.[48]

Celastrol

Celastrol, also known as Thunder God Vine in TCM, is renowned for its remarkable anti-tumor properties.[129] Celastrol has been proved to trigger endogenous apoptosis. Furthermore, it can also initiate the extrinsic apoptotic pathway, as evidenced by the considerable activation of Caspase-8, a critical regulator of the apoptotic pathway. Celastrol has been observed to markedly diminish the viability of H1975 cells in a dose- and time-dependent manner. Cancer cells frequently exploit the chaperone mechanism of Hsp90 to gain a survival advantage, thereby promoting the maintenance of malignant phenotypes and contributing to the phenomenon of "oncogene addiction".[130] In vivo, celastrol was found to substantially reduce the protein expressions of EGFR and Akt, indicating that it inhibits two client proteins of Hsp90. Given that activating EGFR mutations are indispensable for the dysregulation of gefitinib resistance in cells, EGFR degradation can be an effective method of killing cancer cells that primarily depend on EGFR for survival.[61]

Alkaloids

Matrine

Earlier researches have demonstrated matrine exhibits a range of biological activities, including antiviral, anti-inflammatory, antioxidant, and antitumor properties.[131–133] Matrine may help reverse H1975 cell resistance to afatinib by inhibiting the IL-6/JAK1/STAT3 signaling pathway and reducing the expression of Bcl-2.[77]

Evodiamine

Evodiamine (EVO) is the primary constituents of the TCM Evodia rutaecarpa fruit extract and potently inhibits the proliferation of NSCLC cells while exhibiting no toxicity towards normal cells.[134] EVO induces cell apoptosis and inhibits growth in H1975 cells in a manner dependent on transmembrane glycoprotein Mucin 1. EVO has been proven to mitigate T-cell death and curtail PD-L1 expression by neutralizing interferon (IFN). Furthermore, it enhances the functionality of CD8+ T cells, which in turn reduces the levels of mRNA and protein associated with the MUC1 C-terminal domain (MUC1-C). EVO was observed to reduce the tumor weight of H1975 tumor xenograft mice, yet no impact on weight was noted significantly. EVO shows a novel strategy for treating patients with acquired resistance to EGFR-TKIs, whereby it blocks the MUC1-C/PD-L1 axis and elevates CD8+ T cells.[70]

Sinomenine

Sinomenine, extracted from Sinomenium acutum (Thunb). Rehd. et Wils, has anti-inflammatory and immunosuppressive properties. In vitro experiments have shown that sinomenine can reduce hexokinase 2 (HK2)-induced glycolysis in H1975 cells. HK2 is typically overexpressed in several malignancies and is correlated with a poor prognosis. Sinomenine also has significantly affects the sensitivity to chemotherapy and radiation by decreasing AKT activity through blocking the PI3K/AKT signaling pathway.[72]

Apigenin and Oxymatrine

Both apigenin and oxymatrine can dramatically inhibit the survival of H1975 cells. Apigenin and oxymatrine inhibit the proliferation of H1975 cells, with enhanced effects when used in combination. Molecular docking suggests that both compounds strongly bind to EGFR and PLOD2, thereby suppressing EGFR and its downstream signaling pathways. PLOD2, a downstream effector in the EGFR-PI3K/AKT-FOXA1 pathway, is associated with poor lung cancer prognosis.[135] A prior study revealed that PLOD2 is another target of EGFR, and Osimertinib resistance is closely correlated with the PLOD2 overexpression.[53,54]

Sanguinarine

Sanguinarine is one of the main active constituents of Macleaya cordata and has excellent anti-inflammatory, anti-tumor and antioxidant effects.[136] It may be revolved in the JAK/STAT pathway and may induce apoptosis in NSCLC.[137] Sanguinarine selectively degrades EGFR and elevates ROS levels by activating NOX3, thereby disrupting EGFR-mediated proliferative and anti-apoptotic signaling. This highlights the role of NOX3 in EGFR degradation and suggests sanguinarine's potential to enhance the effectiveness of TKI therapy.[80]

Quinone

Plumbagin

Plumbagin (PLB) is the active constituent of Plumbago zeylanica L., and it has multiple anti-tumor effects, including inhibition of tumor cell proliferation, angiogenesis, and metastasis.[138] PLB can directly bind to the ARF1 protein, inducing cell apoptosis, increasing intracellular ROS levels, causing endoplasmic reticulum stress (ER stress) and inducing cell death. In vivo, CD8+ T lymphocytes exhibited a greater activation phenotype and improved effector function after PLB treatment with granzyme B (GRZMB) by producing more IFN, TNF, and GRZMB. PLB (2 mg/kg) inhibited tumor growth in H1975 xenograft mice on day 15, and a significant inhibitory effect was observed between days 15 and day 18. No other toxicities were observed in the study.[43]

Hypocrellin A

Hypocrellin A (HA), a perylene quinoid derived from the fungus *Shiraia bambusicola*, is a potentially effective anticancer drug for photodynamic therapy (PDT) due to its high singlet oxygen quantum yield and strong red absorbing ability.[139] HA promotes apoptosis, inhibits tumor cell invasion, and reduces the activation of key oncogenic pathways, including MAPK, AKT, and STAT3. It achieves this by binding with high affinity to FGFR1, leading to the down-regulation of STAT3 target genes such as Mcl-1, VEGF, and survivin, thereby exhibiting strong anti-tumor potential.[47]

Other

Extraction of Peucedanum Praeruptorum

Bai-hua Qian-hu from the roots of Peucedanum praeruptorum Dunn, is officially recognized in the Chinese Pharmacopoeia and has been used to treat allergic asthma, as well as being utilized as an antipyretic and antitussive agent.[140,141] The extract of Peucedanum praeruptorum (EPP) induces apoptosis and dephosphorylates AKT and STAT3, regulating cell survival and proliferation. Additionally, EPP suppresses MET phosphorylation induced by hepatocyte growth factor (HGF).[62]

Marsdenia Tenacissima Extract

The traditional Chinese medicine Marsdenia tenacissima (Roxb). Wight et Arn., also known as Tongguanteng, is mainly produced in Yunnan province (China) and has been used for centuries. Marsdenia tenacissima (MTE) can suppress the production of hepatoma-derived growth factor (HDGF) and IL-4 in H1975 cells, it repolarizes M2 macrophages towards the M1 phenotype and prevent M2 macrophage infiltration and tumor progression. In addition, MTE can suppress M2 macrophage infiltration and CD206 expression while increasing IL-10 secretion in vivo.[45]

Ephedra Herba Extract

Muhuang, a classic traditional Chinese herb, has the effects of sweating to release the exterior and diffusing the lungs to calm wheezing; this herb is mainly used in the context of external contraction. Ephedrae herba extract (EHE) inhibits tumor growth in a concentration-dependent manner. H1975 activity can be largely inhibited when EHE therapy is administered. Cell proliferation decreases substantially when EHE is combined with osimertinib at the concentration of 4–16 nM. This combination effectively decreased the phosphorylation levels of the MET proto-oncogene receptor tyrosine kinase (RTK), cellular-mesenchymal epithelial transition factor (c-MET), and EGFR, which also prevented the autophosphorylation of c-Met, suggesting the effectiveness of using EHE to treat EGFR with activating mutations (L858R and T790M). Additional in vivo studies are needed to prove the efficacy and safety of this combination.[142] As overuse of EHE can cause adverse effects such as palpitations, sweating, irritation, and insomnia, it is recommended that the dose should not exceed 10 g.[143]

Trichosanthes Kirilowii Extract

Trichosanthes kirilowii extract from the TCM "Gualou", which has the function of clearing heat and dissolving phlegm. In a time- and dose-dependent manner, Trichosanthes kirilowii extract (ETK) suppressed the proliferation of H1975 cells. ETK inhibits cell activity and colony formation in EGFR TKI-resistant NSCLC cells by inducing apoptosis. It also suppresses the SRC/STAT3 pathway, reducing the phosphorylation of SRC and STAT3.[44]

Methanol-Ethyl Acetate of Magnolia Grandiflora

Previous research has revealed the inhibitory effect of Magnolia on many types of cancer, including breast cancer, nasopharyngeal carcinoma, and chronic lymphocytic leukemia.[144,145] The methanol-ethyl acetate extract from Magnolia grandiflora seeds (MEM) demonstrates strong anti-tumor effects on NSCLC by inhibiting cell invasion, migration, and colony formation. It induces apoptosis, reduces Akt levels, and downregulates metastasis-related proteins such as MMP-2, MMP-9, and HIF-1. MEM also exhibits a mild tumor-suppressive effects with minimal toxicity to organs like the kidneys, liver, and lungs.[51]

Bufalin

Bufalin, which has the chemical formula C24H34O4 and a relative molecular mass of 386.52, is a primary active monomer that is isolated from the toad venom used in TCM.[146] The combination of bufalin and gefitinib significantly enhances tumor inhibition and increases tumor cell apoptosis compared to gefitinib monotherapy. Moreover, P-EGFR, P-PI3K, and P-AKT protein synthesis was efficiently decreased by the co-administration of gefitinib and bufalin, indicating inhibition of EGFR-PI3K/AKT signaling pathway.

Pathways Involved in the Effects of Chinese Herbal Medicine on H1975 Cells

Mutation of oncogene receptors often leads to activation of downstream signaling pathways that regulate cell proliferation, the cell cycle and cell survival. Thus, direct regulation of the downstream pathway factors involved influences the development of acquired resistance. The effects of CHM compounds on H1975 cells mainly affect the PI3K/AKT/mTOR, AMPK and IL-6/JAK1/STAT3 pathways, which are important downstream signaling pathways of EGFR.

EGFR-PI3K/AKT Pathway

The PI3K/Akt signaling pathway has been implicated in the development and progression of NSCLC.[147] Aberrant activation of the PI3K/AKT/mTOR pathway is one of the contributing causes of acquired resistance to EGFR TKIs in individuals with adenocarcinoma and EGFR activating mutations.[148] In NSCLC, PI3K plays an important role in promoting EGFR TKI resistance.[149] Studies have shown that the ability of Osimertinib to inhibit H1975 cells is mainly due to its ability to decrease the levels of phosphoinositide-3 kinase, protein kinase B, and phosphorylated Akt.[150] In addition, inhibition of PI3K/AKT/mTOR phosphorylation increases the sensitivity of NCI-H1975/Osimertinib resistant cells (OSIR cells) to Osimertinib.[151] Furthermore, gefitinib resistance in H1975 mice is reversed by NVP-BEZ235, a dual inhibitor of PI3K and mTOR.[152]

IL-6/JAK1/STAT3 Pathway

Cell cycle dysregulation, genomic instability and eventual formation are caused by the IL-6/JAK1/STAT3 signaling pathway. Therefore, the activation of IL-6/JAK1/STAT3 is found in many cancers. IL-6 plays a pivotal role in STAT3-dependent carcinogenesis, and significant correlations have also been found between EGFR mutations and elevated IL-6 expression.[153] STAT3 interferes with Smad3 and induces NSCLC resistance to gefitinib treatment,[154] and the subsequent decrease in STAT3 activation is directly associated with EGFR-TKI resistance.[155] It has also been shown that the inhibitory effect of erlotinib on H1975 cells can be enhanced when endogenous STAT3 expression is inhibited.[28] Fortunately, research has displayed that STAT3 inactivation by ESB can induce apoptosis in EGFR-TKI-resistant cells.[156] Natural products, such as saikosaponin D, can attenuate the phosphorylation of STAT3 to promote the apoptosis of lung cancer cells.[157]

AMPK Pathway

In eukaryotic cells, AMPK (adenosine monophosphate-activated protein kinase), a highly conserved serine/threonine protein kinase, plays a pivotal role in regulating energy metabolism. In NSCLC cells, impaired AMPK activation has been demonstrated to suppress antigen presentation and to increases tumor growth.[158] Metformin, an AMPK activator, has been shown to enhance the sensitivity of H1975 and PC9-GR cells to Osimertinib. The development of Osimertinib resistance is partly attributable to the phenomenon of pro-survival autophagy, which can be mitigated by metformin.[159] A number of organic compounds that activates AMPK has been identified among TCM compounds. One of them is Paris saponin VII (PSVII), which induces AMPK-mediated autophagy directly and inhibits the proliferation of NSCLC cells. However, the related study did not corroborate the hypothesis that PSVII exerts the same effect on H1975 cells.[160] It is therefore imperative to identify natural AMPK agonists as a means of combating TKI resistance.

Discussion

The complexity of EGFR-TKI resistance in NSCLC lies in the intricate crosstalk between signaling pathways and the synergistic potential of multi-targeted interventions. Resistance mechanisms often arise from the activation of parallel or downstream pathways: while EGFR mutations drive survival signaling through the PI3K/AKT and MAPK/ERK pathways, concurrent STAT3 activation further suppresses apoptosis and promotes immune evasion, forming a resilient resistance signaling network. Metabolic reprogramming, such as enhanced glycolysis via the Warburg effect, intersects with these pathways through AMPK-mediated energy-sensing mechanisms, reinforcing resistance by maintaining bioenergetic demands and redox homeostasis.

Moreover, resistance driven by EMT is closely associated with the TGF-β/Smad and Hippo/YAP cascades, which engage in crosstalk with EGFR signaling to enhance invasiveness and stemness. Natural compounds exhibit significant potential to disrupt these interactions through multi-pathway coordination. For instance, celastrol inhibits mutant EGFR kinase activity while destabilizing HSP90-client protein complexes (eg, MET, AKT), thereby blocking both primary and bypass survival signals. Curcumin targets the STAT3/JAK pathway and suppresses angiogenesis markers. Andrographolide not only inhibits STAT3 phosphorylation but also downregulates PD-L1 expression, enhancing CD8+ T cell tumor infiltration and cytotoxicity. Luteolin disrupts the interaction between HSP90 and mutant EGFR and concurrently inhibits the PI3K/Akt/mTOR pathway to overcome resistance. The synergistic effects of drug combinations further amplify therapeutic efficacy. For example, co-treatment with osimertinib and artesunate not only degrades mutant EGFR but also enhances T cell infiltration by inhibiting the TAZ/PD-L1 axis, thereby offering dual targeting of both genetic and immune-mediated resistance. β-elemene activates AMPK to restore apoptosis via energy stress while simultaneously suppressing ERK/NF-κB survival signaling, constituting a “double-hit” mechanism against TKI-tolerant persister cells. These strategies underscore the importance of both vertical and horizontal pathway integration. Vertical targeting focuses on upstream drivers like EGFR, while horizontal targeting blocks adaptive nodes such as STAT3 and metabolic pathways to achieve durable tumor control. Owing to their inherent multi-target pharmacological properties, natural compounds exemplify multi-level interventions against EGFR-TKI resistance in lung cancer, offering a paradigm for next-generation combination therapies in NSCLC.

Nevertheless, a review of the literatures revealed some shortcomings in many recent studies. Firstly, it was evident that deficiencies were present in the experimental design. EGFR-TKIs are more tolerable for patients than chemotherapy, with a relatively low probability and severity of adverse reactions.[161] It is noteworthy that several experimental studies have demonstrated a correlation between the appearance and severity of rash, and the clinical benefit of the treatment in question.[162,163] Previous studies have indicated that EGFR-TKIs can also cause serious adverse reactions including liver dysfunction, stomatitis, paronychia, diarrhea, and interstitial pulmonary disease. While the incidence of Grade 3 and above adverse reactions with TKIs is significantly lower than that with chemotherapy alone, these adverse reactions should not be overlooked in this research. Furthermore, TCM compounds comprise a multitude of chemical constituents, possess multiple targets, and intricate complex mechanisms of action. It is imperative that researchers exercise vigilance regarding the safety of these herbs.

Furthermore, there are explicit dosage requirements for the utilization of this agent, which can only be employed under the guidance of a qualified medical professional and in accordance with the established safe drug dosage range. It is thus imperative that future research be conducted to investigate the safe administration of TCM in vivo and to determine appropriate dosages. A second issue is the absence of joint experiments. A common practice is the combination of TCM compounds with TKIs. A review of the literatures revealed a paucity of experiments examining the effects of combining TKI drugs with Chinese herbal medicine. The combination of Chinese herbal medicine with TKIs is more clinically effective and safe than monotherapy with Chinese herbal medicine. Consequently, this type of research has the potential to offer greater benefits to patients in clinical practice. In real world studies, patients typically receive a decoction comprising multiple Chinese herbal medicines. Consequently, it is meaningful to explore the usage of multiple Chinese herbal medicines in combination with TKIs.

At present, fourth-generation TKIs are not yet available on the market. However, the exploration of Chinese herbal medicine options represents a crucial avenue for enhancing the TCM-based treatment of NSCLC with L858R/T790M mutations, with the aim of improving efficacy and postponing the emergence of Osimertinib resistance. These findings not only extend the current scope of treatment options but also offer potential benefits to patients.

Conclusion

This review systematically explores the therapeutic potential and molecular mechanisms of natural compounds in overcoming resistance to EGFR-TKIs in NSCLC. Beyond highlighting natural compounds as promising strategies for tackling EGFR-TKI resistance, the review also deepens our understanding of their complex mechanisms of action, such as synergistic pathway inhibition, epigenetic modulation, and immuno-metabolic crosstalk. Collectively, this work lays a solid molecular and translational foundation for the development of precision oncology strategies in NSCLC based on natural compound therapeutics.

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Disclosure

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