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Anti-vascular endothelial growth factor (VEGF) herbal medicine associated with non-small cell lung cancer

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Abstract: At present, anti-vascular growth factor drugs are used in cancer treatment to achieve certain efficacy. Based on the current effectiveness of traditional Chinese medicine and extracts for cancer treatment and related research, we therefore summarize the non-small cell lung cancer-related traditional Chinese medicines with anti-angiogenic factors, in order to play the role of traditional Chinese medicine in the treatment of non-small cell lung cancer treatment.

1. Introduction

Recent studies have identified novel anti-vascular growth factor drugs with great potential in the treatment of patients with non-small cell lung cancer, for example, the monoclonal antibody bevacizumab, which targets anti-angiogenic factors, is used in non-small cell lung cancer treatment species. It was found that treatment of metastatic non-small cell lung cancer with EP regimen (cisplatin plus etoposide) in combination with bevacizumab reduced the levels of pro-angiogenic cytokines (VEGF, angiostatin-1 and follicle inhibitor) and inflammatory cytokines (interferon (IFN) γ, IL4 and IL17) compared to the conventional EP regimen, showing potent anti-angiogenic effects and anti-tumor properties[1].The study found a positive correlation between the reduction in mean tumor blood flow detected in six patients with non-small cell lung cancer treated with bevacizumab plus chemotherapy compared to six patients with non-small cell lung cancer treated with bevacizumab without bevacizumab [2]. Compared to patients with non-small cell lung cancer without craniosynostosis, bevacizumab may be more beneficial for use in patients with non-small cell lung cancer who develop brain metastases by inhibiting angiogenesis and minimizing vasogenic edema [3]. The combination of bevacizumab and the tyrosinase inhibitor erlotinib significantly prolonged tumor-free survival in advanced EGFR-mutant non-small cell lung cancer [4]. Recent studies have identified cardiotoxicity, neurotoxicity and vascular toxicity of modern cancer treatments, such as venous thromboembolism, acute vasospasm, acute thrombosis and accelerated atherosclerosis [5-7]. For example, bevacizumab produces adverse effects such as hypertension, cardiac ischemia, and arterial thrombosis [8]. Tracheoesophageal fistulae have occurred after radiotherapy for non-small cell lung cancer in combination with bevacizumab [9]. At the same time, the application of anti-

angiogenic factor drugs is associated with more side effects such as skin reactions in the hands and feet [10]. At the same time, anti-angiogenic factor drugs are more costly, causing a great financial burden for patients.

Chinese herbs and extracts have been found to have possible anticancer potential, and studies have found that danshen, scutellaria, turmeric, and ginsenosides have properties that inhibit tumor angiogenesis [11]. Salviae were found to significantly decrease monoamine oxidase (MAOB) activity, attenuate NF-κB signaling, and enhance the sensitivity of radiotherapy for non-small cell lung cancer [12] . Honokiol (HNK), extracted from Magnolia officinalis, was found to inhibit the migration of A549 and H460 cells significantly enhanced by treatment with TNF-α+TGF-β1, inhibit C-FLIP expression in cells, which in turn may affect downstream effector NK-κB signaling, leading to the speculation that HNK may inhibit the motility and migration of non-small cell lung cancer cells [13]. In the present study, we found that Chinese toadstool (CB) downregulates the negative transcription factor c-Jun of ENKUR by inhibiting PI3K/AKT signaling and suppresses the expression of MYH9, the binding protein of ENKUR, which in turn ultimately attenuates cisplatin resistance through a series of responses, thus speculating that Chinese toadstool has potential antitumor properties by reducing cisplatin resistance, migration and invasion in lung adenocarcinoma (LUAD)[14] .The Chinese herbal combination of vincristine + cisplatin/carboplatin was more efficacious compared to the control group in relieving adverse effects such as vomiting, fatigue, pain, dry mouth and diarrhea and reducing hematological toxicity, as well as relieving patients from chest pain and hemoptysis discomfort [15]. Various angiogenic factors, including vascular endothelial growth factor (VEGF) and 139 basic fibroblast growth factor (bFGF), were found to play a role in promoting tumor angiogenesis during tumorigenesis [16]. In a related retrospective study, VEGF was found to be immunoreactive in surgically resected specimens (T1-3, N0-2) from 104 patients with operable non-small cell lung cancer, and it was hypothesized that the expression of vascular endothelial growth factor (VEGF) in tumor cells was associated with angiogenesis and poor prognosis of non-small cell lung cancer [17]. Therefore, based on the current effectiveness of Chinese herbal medicines and extracts in the treatment of cancer and related studies, herbal medicines with anti-angiogenic factors associated with non-small cell lung cancer are therefore summarized with a view to playing a role in the treatment of non-small cell lung cancer therapy with Chinese herbal medicines to reduce the socioeconomic burden for the benefit of non-small cell lung cancer patients.

2. Chinese medicine and derivatives

2.1 Scutellaria baicalensis

The main components of Scutellaria baicalensis include flavonoids, which are anti-inflammatory, antibacterial, antiviral, anticancer, and hepatoprotective [18]. Scutellaria baicalensis fights lung cancer through five mechanisms: induction of apoptosis, cell cycle arrest, inhibition of proliferation, blocking invasion and metastasis, and overcoming drug resistance [18-19]. Baicalin decreased VEGF expression in lung cancer A549 cells, and studies have shown that baicalin inhibited invasion and migration of lung cancer A549 cells and angiogenesis in xenograft tumors in nude mice [20]. Baicalein significantly reduced the proliferation of A549 cells and SKMES1 cells (squamous carcinoma) in adenocarcinoma, and in vivo experiments in mice showed that baicalein reduced the growth of H-460 non-small cell lung cancer cells in a dose-dependent manner, not containing subtypes of non-small cell lung cancer, and the expression of both FGFR-2 and VEGF involved in angiogenesis was significantly increased in H-460 xenografts [21]. Baicalein and baicalein inhibited the migration of human umbilical vein endothelial cells HUVECs to fibroblast growth factor bFGF [22]. Baicalein inhibited the expression of Id1 protein, angiogenesis-associated protein (VEGF-A), etc., while upregulating epithelial markers (e.g., E-calmodulin), and inhibited tumor growth in in situ

human non-small cell lung cancer xenografts by targeting the Src/Id1 pathway [23].

2.2 Marsdeniae tenacissimae (MTE)

Marsdeniae tenacissimae**(**MTE**),** The traditional name in Chinese medicine is Tongguan vine, which is the main ingredient of the anti-cancer pine injection [24].Modern pharmacological studies of Tongguan vine have proved that it has 196 chemical components such as steroids, triterpenes and organic acids, which have been widely used in the treatment of stroke asthma, bronchitis, tonsillitis, pharyngitis, cystitis, and pneumonia, where steroids have multiple drug resistance reversal, anti-tumor, anti-angiogenic, immunomodulatory, and anti-HIV activities [25]. Tongguan vine extract in combination with chemotherapy is superior to chemotherapy alone in the treatment of advanced non-small cell lung cancer and improves the efficiency of treatment and patient quality of life [26]. MTE inhibits proliferation by attenuating CCL-2-mediated VEGF/VEGFR2 interactions and triggers PKCδ-induced p53-dependent mitochondrial pathway, enhancing apoptosis [27]. In addition, the anti-non-small cell lung cancer effects of six C21 steroidal saponins were shown by network pharmacology studies to be mainly involved in HIF-1 signaling, PI3K-Akt signaling, VEGF signaling, EGFR tyrosine and other pathway kinase inhibitor resistance and Ras signaling in cancer [28].

2.3 Nuciferine (NF)

nuciferine**(**NF**),** NF is a component with antiviral and anticancer effects extracted from lotus root, NF significantly inhibited the proliferation of NSCLC cells under the effect of nicotine, inhibited the activity of Wnt/β-linked protein signaling pathway, enhanced the stability of axial proteins, and induced apoptosis, i.e., NF downregulated the expression levels of β-linked protein and its downstream targets c-myc, cell cycle protein D and VEGF-A, NF also decreased the Bcl-2/Bax ratio and promoted apoptosis [29]. In vitro NF promotes the production of PDGF-BB and enhances the associated angiogenic activity by inhibiting the expression of osteoclast-specific genes and proteins through inhibition of MAPK and NF-κB signaling pathways.Nuciferine restrained the expression of osteoclast-specific genes and proteins, promoted PDGF-BB production and potentiated related angiogenic activities by inhibiting the MAPK and NF-κB signaling pathways in vitro[30]**.** In addition, NF attenuates weight gain, hyperlipidemia and hepatic steatosis by regulating lipid metabolism gene expression [31].

2.4 Rhodiola rosea

Rhodiola rosea is a genus of the Tianidae family with antioxidant, anti-inflammatory, immunomodulatory, anti-fatigue, neuroprotective, hepatoprotective, renal protective, antidepressant, and anticancer effects [32]. In addition, Rhodiola rosea reduces oxidized low-density lipoprotein (ox-LDL)-induced endothelial damage alleviating atherosclerosis [33]. By establishing a network pharmacological study related to non-small cell lung cancer, it was found that the non-small cell lung cancer effects of rhodiola glycosides were mainly manifested in the regulation of apoptosis, angiogenesis and inflammation, and rhodiola glycosides inhibited tumor angiogenesis and controlled cell metastasis by regulating VEGF and MMP2, downstream mediator eNOS and influencing VEGF expression, in addition rhodiola glycosides controlled cell metastasis by regulating PI3K/AKT signaling pathway (hsa04151), MAPK signaling pathway (hsa04010) and NF-κB signaling pathway (hsa04064) in target distribution, affecting cell proliferation, apoptosis and inflammation [34].

2.5 Astragalus

Astragalus most herb is found in Shennong Ben Cao Jing and contains various chemical components such as astragalus polysaccharide, astragaloside, flavonoids, etc. Astragaloside IV has antioxidant, antiapoptotic, and antiviral effects and is used in cardiovascular, cerebrovascular, digestive, and cancer diseases [35]. Studies have shown that high doses of astragaloside (10, 20, and 40 ng/ml) inhibited the growth of NSCLC cells, and in vitro experiments demonstrated that astragaloside IV was able to enhance chemosensitivity to cisplatin by inhibiting B7-H3 [36]. Astragaloside IV may sensitize NSCLC cells to gefitinib by modulating SIRT6 [37]. Astragaloside IV sensitizes NSCLC cells to cisplatin by inhibiting endoplasmic reticulum stress and autophagy [38].

2.6 Cordyceps sinensis

As a highly valued traditional Chinese medicine, studies have shown that Cordyceps sinensis has oxygen radical scavenging, anti-aging, endocrine, hypolipidemic, anti-atherosclerotic and restorative effects on sexual function [39]. The expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) was significantly reduced in H157 cells by flow cytometry when Cordyceps polysaccharide was combined with chemotherapy compared with cells treated with cisplatin alone [40]. Cordyceps aqueous extract enhanced the antitumor effects of DDP and attenuated the treatment-related toxicity of NSCLC through the IκBα/NFκB and AKT/MMP2/MMP9 pathways, while NF-κB activation upregulated the expression of vegf-responsive genes in cancer cells [41]. In addition, Cordyceps inhibited proliferation, induced apoptosis, and led to G2/M phase arrest in human non-small cell lung cancer cells, Cordyceps also induced cell cycle arrest in G0/G1 phase and increased apoptosis [42-43].

2.7 Ginsenoside

Ginsenosides are a key active component of ginseng and belong to the triterpenoid saponins group, especially containing Rg3 with great anticancer properties, which was found to have anti-inflammatory, antioxidant, anticancer, anti-fatigue, anti-aging and vasodilatory effects [44-46]. Ginsenoside Rh2 (G-Rh2) converted tumor-associated macrophages (TAM) from M2 subpopulation to M1 subpopulation in the microenvironment, decreased the expression level of VEGF, and inhibited the migration of lung cancer A549 and H1299 cells, and presumably ginsenoside Rh2 inhibited the migration of non-small cell lung cancer [47]. Ginsenoside Rg3 has anti-lung cancer properties by inhibiting epithelial mesenchymal transition (EMT) and lung cancer invasion through down-regulation of fucosyltransferase IV (FUT4), mediating EGFR inactivation and blocking MAPK and NF-κB signaling pathways [48]. Ginsenoside Rg5 has good anticancer properties for human A549 cells [49]. Total ginsenosides extract (TGS) combined with mitomycin C was used in non-small cell lung cancer A549 cells, and the combination was dependent on the DNA repair protease Rad51, and the combination reduced the concentration of mitomycin C, further reducing chemotherapeutic drug side effects and exerting a synergistic anti-non-small cell lung cancer effect [50]. Modern network pharmacological studies have shown that the immune response of ginseng leaves against lung cancer may be related to lipopolysaccharide, response to oxidative stress, PI3K-Akt, MAPK, and TNF pathways, that ginseng leaves are associated with multiple targets such as VEGFA in the treatment of lung cancer, and that ginseng leaves are involved in apoptosis of non-small cell lung cancer cells and can treat lung adenocarcinoma [51]. Therefore, it is hypothesized that ginsenosides have the effects of improving tumor microenvironment, improving chemotherapeutic drug sensitivity, reducing gas side effects, decreasing VEGF expression, and reducing metastasis and invasion in non-small cell lung cancer.

2.8 Myricanol

Myricanol has anti-inflammatory, anti-cancer, anti-androgenic and Alzheimer's disease reversal effects [52]. Myricanol derivative 3,5-dimethoxy-4-hydroxyjanumol has a protective effect against oxidative stress-induced myocardial cell injury by reducing oxidative stress and inhibiting the inflammatory response in cardiomyocytes. Myricanol derivative has a possible protective effect against myocardial ischemia [53]. The growth inhibition of human leukemia cells HL-60 by Myricanol 5-fluorophenoxy ether (5FEM) [54]. Myricanol downregulated VEGF in mRNA expression in lung adenocarcinoma A549 transplantation tumor nude mice in a dose-dependent manner, and apoptosis-positive cells were significantly increased in Myricanol -treated tumor tissues compared to the polyethylene glycol 400 lysate group. It was shown that Myricanol downregulated VEGF mRNA expression in a dose-dependent manner in lung adenocarcinoma A549 transplantation tumor nude mice and, at the same time, significantly slowed down the growth of non-small cell lung cancer [52]. Myricanol alcohol 5-fluorobenzyl ether is a derivative of Myricanol, and 5FEM significantly inhibited the growth of A549 Homo BIRC5 growth cells; induced apoptosis; increased G0/G1 population; decreased $\Delta\psi m$; and inhibited cell migration. Inhibition of colony composition upregulated caspase-9, P21 and Bax expression levels; downregulated PARP, survivin and Bcl-2 expression levels, and 5FEM had the ability to regulate the survivin pathway, thereby inhibiting the growth of human lung adenocarcinoma A549 cells in vitro [55]. Therefore, it is hypothesized that Myricanol and its derivative Myricanol 5-fluorophenoxy ether contribute to the inhibition of non-small cell lung cancer tumor growth.

2.9 Schisandra chinensis and derivatives

Modern pharmacological studies have revealed that Schisandra chinensis and its derivatives have antioxidant, myocardial damage cell protection, antitumor, intestinal flora and lipid metabolism effects [56-57]. Various derivatives were isolated from Schisandra chinensis: quinic acid derivatives, lignans and derivatives, phosphonic acid derivatives and other derivatives, and Schisandra a, Schisandra b, Schisandra (schisandrathera C), Schisandra d and lignans components isolated from Schisandra leaves were found to be cytotoxic to prostate cancer and breast cancer cells [58]. Schisandrathera B (Sch B) inhibits the invasion and migration of A549 cells by downregulating the expression of HIF-1, VEGF, MMP-9, and MMP-2; therefore, Sch B has strong antitumor activity. sch B significantly inhibited the proliferation of A549 cells at 48 h ($P<0.05$) and treated different time cycles with different doses of Sch B in a dose- and time- dependent inhibition of A549 cell proliferation and dose dependent inhibition of A549 cell clone formation, and Sch B induced cell cycle arrest in G0/G1 phase, triggered apoptosis and attenuated cell invasion to exert activity [59]. In addition, Schisandra chinensis A (Sch A), a lignan compound isolated from Schisandra chinensis, synergizes with the EGFR receptor inhibitor gefitinib to inhibit cell growth, induce HCC827/GR cell cycle arrest and apoptosis, and enhance the efficacy of gefitinib by inhibiting IKKβ/NF-κB signaling in non-small cell lung cancer [60]. Therefore, it is hypothesized that pentosidine can downregulate VEGF expression in mRNA and pentosidine derivatives have strong antitumor activity, while enhancing tyrosine kinase inhibitor sensitivity and inhibiting the growth of non-small cell lung cancer.

2.10 Taspine

Taspine isolated from Radix Leonticis downregulates VEGF secretion in human non-small cell lung cancer (A549 cells) and also inhibits angiogenesis by suppressing HUVEC proliferation and migration [61].

2.11 Sotisoflavones

Sotisoflavones, which are derived from the Chinese herbal medicine sotisoflavones, are flavonoids. Sotisoflavones reverse EMT, thereby inhibiting the migration and invasion of A549 cells. This process may inhibit PI3K/AKT and TNF-α/NF-κB signaling pathways and downregulate HIF-1α expression to reduce VEGF expression and downregulate angiogenesis inhibitor expression [62].

2.12 Horsetail Pine Bark Extract

The main constituents of horsetail pine bark extract (PMBE) are flavonoid chemotactic components, especially proanthocyanidins, and flavonoids can inhibit the abnormally high expression of histone proteinase B (CatB) in some tumor cells [63]. Horsetail pine bark phenolic extract (PEPB) may be a natural antioxidant with antioxidant, immunomodulatory and anti-breast cancer activities [64]. Horsetail pine bark extract (PMBE) induced apoptosis in hepatocellular carcinoma cells and cervical cancer cells, and Horsetail pine bark extract significantly inhibited the growth of lung cancer A549 cells while limiting their metastasis and invasion [65]. Therefore, it is hypothesized that horsetail pine bark extract (PMBE) has the potential to inhibit the growth and metastasis of non-small cell lung cancer.

3. Conclusions and Discussion

Lung tumor angiogenesis is closely related to the inflammatory microenvironment, foreign bodies, thrombin, and gene mutations, all of whom are involved in the non-small cell lung cancer angiogenesis process through regulation of VEGF [66-69]. For example, IL-17 in non-small cell lung cancer promotes non-small cell lung cancer angiogenesis through STAT3/GIV activation of VEGF production [66]. Exosomal human umbilical vein endothelial cell miR-3157-3p increases VEGF expression in endothelial cells by targeting TIMP/KLF2, thereby promoting angiogenesis and increasing vascular permeability, and exosomal miR-3157-3p promotes metastasis of non-small cell lung cancer in vivo [67]. The overall survival of patients with non-small cell lung cancer (NSCLC) is associated with vasculogenic mimicry (VM), and thrombin expression is closely related to VM formation, which was found to be induced by a PAR-1-mediated NF-κB signaling cascade. Clinicopathological analysis confirmed that NSCLC patients with positive thrombin/high PAR-1 expression had the worst prognosis and were most prone to VM formation [68]. The mutational profile of RFS analysis detected a genome enriched in VEGF signaling pathway, mainly KDR, SH2D2A, SRC, and KRAS, whose mutational status showed a significant association with postoperative recurrence in stage I non-small cell lung cancer [69]. It was found that non-small cell lung cancer-related anti-vascular endothelial growth factor (VEGF) herbal medicines among Astragalus, Ginsenoside and Cordyceps belong to the category of tonic medicines in Chinese medicine, Rhodiola rosea has the effect of activating blood circulation and resolving blood stasis, which is related to thrombin first off in Western medicine, and the above three medicines have immunomodulatory effects with Rhodiola rosea and Tongguan vine extracts, and Chinese medicine theory advocates that qi and blood are related to each other, and tonic medicines replenish qi and nourish blood, so it is presumed that the above tonic and blood activating The anti-non-small cell lung cancer properties of Chinese herbs are closely related to inflammation, blood clotting mechanism, and immune function. The drugs such as Thornybush, Scutellaria baicalensis, Sotisuflavone, and Horsetail pine extract contain flavonoids, and modern pharmacology suggests that flavonoids regulate key signaling pathways mediating the migration and progression of invasion and metastasis of cancer cells involved, as well as regulate the expression of genes related to cancer first, the improvement of inflammatory status, while enhancing the effect of conventional chemotherapeutic drugs [70].

Therefore, the above drugs may have anti-vascular growth factor effects to treat non-small cell lung cancer. However, the evaluation criteria for the efficacy of non-small cell lung cancer are not uniform so far, so it is difficult to unify the evaluation criteria for the efficacy of TCM with anti-vascular growth factor effect to treat non-small cell lung cancer, and there is still a need to discover such drugs and their efficacy criteria in clinical practice to contribute to the further treatment of non-small cell lung cancer.

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