Chapter 12

Antitumor Effect of Natural Product Molecules against Lung Cancer

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67241

Abstract

Lung cancer treatment remains difficult because of multidrug resistance and adverse effects, and natural product molecules show powerful activity in lung cancer with few side effects. The molecular targets and efficacy of natural product molecules remain unclear. We described the molecular regulation of natural product molecules with antitumor activities, the antilung cancer activities and the clinical trials for lung cancer treatment of natural product molecules. The results support the updated systemic information on the use of natural product molecules to prevent cancer progression and their constituents for lung cancer treatment.

Keywords: lung cancer, natural product molecules, antitumor activity

1. Introduction

Lung cancer treatment remains difficult because of multidrug resistance and adverse effects. Natural product molecules represent an attractive approach for lung cancer therapy with few side effects but high treatment outcome. Various natural product molecules have proven to be useful and effective in sensitizing conventional agents. Several natural product molecules can prevent the side effects of chemotherapy. Moreover, natural product molecules can improve the quality of life (QoL) and prolong the survival time of lung cancer patients. In this chapter, we summarize the molecular regulation mechanisms of natural product molecules and their antitumor effects on lung cancer *in vitro* and *in vivo*.

In lung cancer treatment, the molecular targets and efficacy of natural product molecules remain unclear. Thus, we reviewed the antitumor activities of natural product molecules in lung cancer

therapy. This chapter is mainly divided into three parts: the molecular regulation of natural product molecules with antitumor activities, the antilung cancer activities of natural product molecules *in vivo*, and the clinical trials on natural product molecules for lung cancer treatment.

On the basis of our critical analyses, we suggest the potential of natural product molecules that have been traditionally used for lung diseases, including cancer, and the discussion of data from *in vitro* or *in vivo* laboratory experimental models and clinical trials. We suggest that natural product molecules can be potent anticancer agents for lung cancer treatment and prevention by regulating multimolecular targets. The effects of natural product molecules are involved in angiogenesis, metastasis, and severe side effects.

Lung cancer is the leading cause of cancer death worldwide. Small-cell lung cancer (SCLC) and non–small-cell lung cancer (NSCLC) are the two main types of lung cancer. Smoking can induce most kinds of lung cancer. In addition, vinyl chloride, arsenic, cadmium, beryllium, chloride, and nickel chromates contribute to the occurrence of lung cancer. For lung cancer patients who are nonsmokers, their cancer is usually caused by a combination of genetic factors, as well as exposure to radon gas and air pollution [1, 2]. For lung cancer, early diagnosis is very important for patients to improve their survival rate. The cause of lung cancer did not show any obvious symptoms until the cancer began to metastasize to other organs.

Chemotherapy, radiotherapy, and surgery are the most widely used strategies in lung cancer treatment. However, standard chemotherapies present severe toxicity for patients and may result in limited survival benefit. Given that phytochemicals and antitumor herbs are less toxic, these agents are used to treat lung cancer, and the outcome has attracted recent reports and investigations [3]. To date, antilung cancer herbs have included 130 Chinese herbal medicines with effective treatment effects. These herbs are classified on the basis of their actions: (1) clearing heat and toxin, (2) resolving dampness and phlegm, (3) regulating blood and Qi, (4) reinforcing Qi, and (5) nourishing Yin through their ethnopharmacological efficacies.

In this chapter, we discuss the ethnopharmacological effects of natural product molecules focusing on metastasis, angiogenesis, apoptosis, and clinical trial efficacy. In these reviews, the results support the updated systemic information on the use of natural product molecules to prevent cancer progression and their constituents for lung cancer treatment.

2. Molecular regulation of natural product molecules with antitumor activities

To develop useful agents for cancer therapy, the unique activity mechanisms of natural product molecules should be studied. The molecular mechanisms of natural product molecules with anticancer activities are important for the development of many drug-targeted therapies for cancer treatment [4]. Molecular biology methods for high-risk individuals during early diagnosis, screening, and identification can help determine the prognosis of innovative treatment and provide a novel point of view [5]. Significantly, target molecules should be considered for lung cancer treatment.

2.1. Apoptosis and natural product molecules

Apoptosis involves a series of morphological alterations, such as plasma and nuclear membrane blebbing, cell shrinkage, dissolution of nuclear lamina, and biochemical processes, which are responsible for the activation of apoptosis [6]. In Chinese medicine, the fruit and roots of *Toona sinensis* (Meliaceae) have been used for cancer therapy. Toona displayed glucose uptake in 3T3-L1 adipocyte differentiation of fat and enhanced the antidiabetic activity [7]. *T. sinensis* leaf extract (TSL-1) inhibition of lung adenocarcinoma cell proliferation after 24 hours can mediate apoptosis at 0.5 or 1 mg/mL. *Ocimum gratissimum* (OG) (Lamiaceae) is a perennial aromatic herb with antibacterial and antidiabetic activity in Taiwan and is traditionally used to treat gastrointestinal diseases. OG can activate apoptotic signaling molecules, such as caspase-3 and caspase-9, in A549 cells at a concentration of 0.5 or 0.8 mg/mL; thus, OG is a potentially useful candidate [8]. In lung cancer cell apoptosis, medicinal plants from many biologically active compounds are also known as potent inducers. Acacetin flavonoid polyphenol compound (5,7-dihydroxy-4′-methoxy-flavonoids) from *Robinia pseudoacacia* (legumes) can inhibit A549 cell proliferation (IC50 = 9.46 μm). By upregulating p53 and p21/WAF1 proteins, acacia-induced apoptosis and cell cycle at the concentrations of 5 or 10 μM in A549 cells [9]. Dihydroartemisinin (DHA) is a derivative of artemisinin from *Artemisia annua* Altai Michael (Asteraceae) and is used to treat malaria; DHA can also induce apoptosis in human lung cancer cells. PG490 (triptolide), a diterpene triepoxide from *Tripterygium wilfordii* (Celastraceae), was significantly sensitized to Apo2L/TRAIL-induced apoptosis, but it did not significantly induce cell death in A549 cells. Acutiaporberine is a bisalkaloid from the pointed leaves of Thalictrum (Ranunculaceae); ritterazine B is one of the ritterazine analogues from *Ritterella tokioka* (Polyclinidae), and ursolic acid is a pentacyclic triterpene from *Hedyotis diffusa* (Rubiaceae); these agents were all reported to induce apoptosis *in vitro*. Ginseng extract (EAG) (Panax ginseng C.A. Meyer) exerts anticancer effects on Lewis lung carcinoma cells (LLC) and demonstrates weak activity in breast cancer and liver cancer cells; the results showed that lung cancer cells may be more likely to prompt treatment by EAG.

By modulation of ERK-p53 and NF-κB signaling, EAG revealed inhibition *in vitro* and *in vivo* of mouse LLC. Traditional Chinese herbal medicine significantly inhibited the proliferation of A549 cells, partly because of the inhibition of NF-κB activation induced by tumor necrosis factor alpha (TNF-α) [10]. H460 cell viability was reduced by plumbagin from *Plumbago indica*, and the A549 cell survival rate decreased to 17.6% at 15 μM [11]. By inhibiting the survival proteins Akt, NF-κB, Bcl-2, and survivin in H460 cells, plumbagin can induce apoptosis. In addition, many traditional herbs have induced apoptosis in lung cancer cells; other biologically active substances have also induced apoptosis: glossogin from *Glossogyne tenuifolia* (Asteraceae), a novel ginsenoside 25-OCH(3)-PPD from *Panax notoginseng* (Araliaceae), deguelin from *Lonchocarpus utilis* or *Lonchocarpus urucu* (Fabaceae), and elemene from *Curcuma kwangsiensis* (Zingiberaceae) [12].

2.2. Inhibitory effects of natural product molecules on angiogenesis and metastasis

Among the contributing factors to the spread and growth of lung cancer, angiogenesis is the most important process because it involves the growth of new blood vessels from preexisting

vessels. Angiogenesis is associated with the development and spread of lung cancer because it influences the growth of novel blood vessels [13]. Thus, blockage of angiogenesis is considered an important therapeutic target for lung cancer. In the past decade, clinical trials have been conducted on angiostatin, endostatin, solimastat, bevacizumab, and angiozyme-targeting vascular endothelial growth factor (VEGF) as a key factor of angiogenesis. Selected VEGF targets have shown survival benefits in patient therapy [14]. VEGF is also related to other indirect angiogenic factors, such as basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and tumor growth factor alpha (TGF-α) [15].

As a medicinal herb, *Ganoderma lucidum* (Ganodermataceae) is a basidiomycete white rot fungus, which is helpful to the treatment of various diseases such as cancer, HIV infection, diabetes, asthma, and ulcers, as demonstrated in Korea, China, and Japan [16]. Thus, many experts suggest the use of *G. lucidum* for prostate, skin, ovarian, and colon cancer therapy [17–19].

The growth of PG cells in Balb/c nude mice significantly inhibited *G. lucidum* polysaccharides. For human umbilical vein endothelial cells (HUVECs), *G. lucidum* polysaccharides also inhibited cell proliferation. Under hypoxic condition, *G. lucidum* polysaccharides inhibited the secretion of VEGF in lung cancer cells. By using chick chorioallantoic membrane (CAM) assay, *G. lucidum* polysaccharides were proven to exert an antiangiogenic effect on Balb/c mice. Overall, these results suggest that *G. lucidum* polysaccharides inhibited vascular cell proliferation in HUVECs. In human lung carcinoma PG cells, *G. lucidum* polysaccharides also reduced the secretion of VEGF. Generally, clinical researchers unexpectedly found that *G. lucidum* polysaccharides might positively influence chemo/radiotherapy by combining these compounds with the subgroups of advanced lung cancer patients, resulting in reversed immunosuppressive effects on traditional cancer therapy [20]. Although the antitumor activity against lung cancer has been recognized, we need to study its efficacy, safety, optimal concentration, and molecular targets for further research. The effect of VEGF alone or in combination with current therapies for lung cancer is also very important to be investigated through future pharmacokinetic research on animals and humans.

The most characteristic aspect of malignant neoplasm is metastasis, which is the leading cause of death in cancer patients [21]. Tumor cell dissociation, intravasation, invasion, and distribution to distant organs arrest cells in small vessels, resulting in adhesion to endothelial cells, extravasation, invasion of the target organ, and proliferation, which are all related to tumor metastasis. matrix metalloproteinases (MMPs) are related to metastasis and cancer invasion and are proteolytic enzymes in the extracellular matrix (ECM). MMP-2 and MMP-9 significantly influence the metastatic processes among the MMP family [22, 23].

2.3. Reversion of multidrug resistance

The largest difficulty of chemotherapy against cancers is multidrug resistance (MDR) [24]. Cellular overproduction of p-glycoprotein (p-gp) is one of the influencing factors leading to MDR because it can transport various anticancer drugs outward the cell. To date, a series of compounds to reverse MDR by interfering with the p-gp function have been determined [25–27]. However, some MDR reversal agents may lead to the change of pharmacokinetics and even cause serious side effects. Many anticancer drugs such as docetaxel, gemcitabine,

and vinorelbine can overexpress MDR-associated proteins (MRPs), including pgp. Although this effect is helpful for inducing MDR in the treatment of NSCLC, new MDR reversal agents should be developed to avoid MDR and improve the effects of lung cancer therapy.

Stephania tetrandra (Menispermaceae) comprises a herbal formula, which is also called "Supplement energy and nourish lung" (SENL) in herbal medicines. Both *S. tetrandra* and *G. lucidum* (Ganodermataceae) demonstrate a MDR-reversal potential in SW1573/2R 120, adriamycin (ADM)-resistant lung cancer cells, and valproic acid (VPA) MDR SCLC. Solamargine (SM) suppressed MRPs in lung cancer cells, although SM is traditionally used to treat chest pains, pleurisy, pneumonia, toothache, and sore throat in India because of the major steroidal glycoalkaloid from *Solanum incanum* (Solanaceae). SM enhanced the sensitivity of apoptosis induction in tumor necrosis factor (TNF) and cisplatin-resistant lung cancer cells. After combining the treatment of SM and epirubicin, we observed that the apoptosis effect of chemotherapy was improved in A549 cells [28, 29]. Hence, we believe that SM is a potential MDR-reversal agent [30]. A test also showed that additional bioactive phytochemicals might be potential MDR-reversal agents, which include a novel monoketone curcumin analog, EF24 from *Curcuma longa* (Zingiberaceae), emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) from *Rheum palmatum* (Polygonaceae), and elemene from *C. kwangsiensis* (Zingiberaceae) [31].

2.4. Reactive oxygen species (ROS) and lung cancer therapy

Recently, ROS signaling became the focus of research on lung cancer as well as other cancer therapies [32]. In recent lung cancer therapies, targeting ROS signaling was thought to be a striking method [33]. Notably, smoke-oxidative stress results in DNA damage and restrains survival signaling, which make proliferation out of control during the transfer of lung epithelial cells [34–36]. Few studies have shown that some herbal extracts and their components can eliminate active oxygen in lung cancer cells.

In Korea, people maintain oral health by using *Polygonum cuspidatum* (Polygonaceae) because of its effect in reducing oral microorganisms; Koreans also use *P. cuspidatum* in the treatment of arthritis and urinary diseases [37]. *P. cuspidatum* extract contains alkaloids, phenolics, and sterol/terpenes and induces biological activities such as anti-inflammation, antioxidation, and anticancer effects [38]. In A549 and H1650 cells, the ethanol and ethyl acetate extracts of *P. cuspidatum* can eliminate 1,1-diphenyl-2-hydrazyl (DPPH) and hydroxyl radicals. The ethyl acetate fraction (EAF) of wampee peel [*Clausena lansium* Skeels (Rutaceae)] is obtained from a species of strongly scented evergreen trees in Southeast Asia. Similarly, in comparison with cisplatin, the EAF of wampee peel exerted increased antioxidant and anticancer effects on A549 lung cancer cells, SGC-7901 gastric cancer cells, and HepG2 liver cancer cells. Thus, wampee peel should be studied to develop a natural antioxidant and pharmaceutical supplement because of the DPPH radical scavenging activity, reducing power, and superoxide scavenging activity.

Recently, Lawless et al. advised in their review paper that histone deacetylase (HDAC) can significantly regulate the oxidative stress pathways in the development of cancer in NSCLC [39–41]. The authors advised that HDAC can be consumed in several common foods such as sulforaphane from *Brassica oleracea* (Brassicaceae), curcumin from *C. longa* L. (Zingiberaceae),

and epigallocatechin 3-gallate (EGCG) from *Camellia sinensis* (Theaceae) to combat NSCLC and chronic obstructive pulmonary disease (COPD). Nevertheless, further research on HDAC inhibition is necessary to develop more efficient antitumor drugs from herbal medicine. The mechanism and molecular targets of natural product molecules against lung cancer were shown in **Figures 1** and **2**.

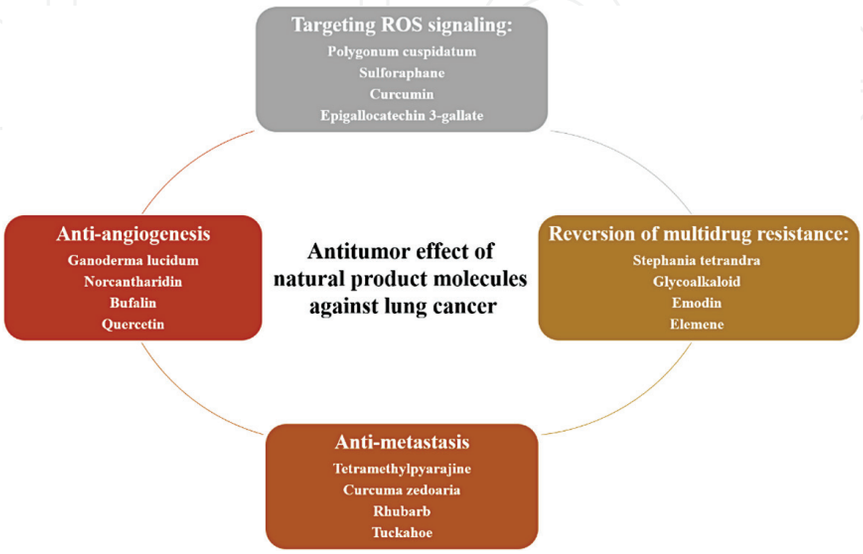

Figure 1. Mechanism of natural product molecules against lung cancer.

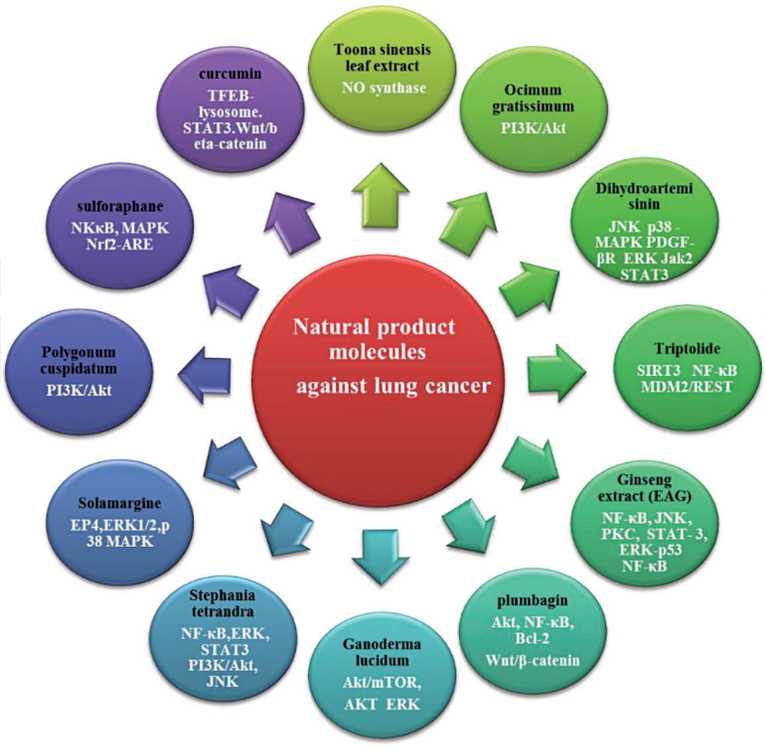

Figure 2. Targets and/or pathways effected by natural product molecules against lung cancer.

http://dx.doi.org/10.5772/67241

3. Antilung cancer natural product molecules in the body

The allogeneic graft model or mice xenograft is a valuable tool in cancer biology evaluation of novel anticancer activity of drug(s). Antitumor activity test is employed to measure the inhibition of the tumor growth and survival time. In vivo mouse models and some active natural product molecules also showed influence on antilung cancer.

3.1. Green tea polyphenols and lung cancer

Tea extract from the plant *C. sinensis* is the most common beverage for consumption worldwide. Important data from different studies provide evidence that drinking tea can prevent carcinogenic effects [42, 43]. All activities related to a major component of green tea exert the effects of (−)-epigallocatechin gallate (EGCG). Some mechanisms showed that EGCG-induced apoptosis and cell-cycle arrest modulation in carcinogen-metabolizing enzymes and regulate cellular signaling pathways and inhibit transcription factors in cancer cells, resulting in the inhibition of cancer development, which facilitated the prevention and treatment by green tea and its composition, particularly EGCG.

Green tea can help prevent and treat lung cancer, especially EGCG and guanosine triphosphate (GTP). Dietary supplementation of EGCG (0.1, 0.3, and 0.5%) inhibited tumor growth in nude mice implanted with thymus H1299 cells. EGCG treatment increased phosphorylated histone 2A variants X and tumor cell apoptosis, as well as oxidative DNA damage assessment of the formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG). This finding presents the first evidence of EGCG induction of ROS generation, leading to tumor cell DNA oxidative damage. EGCG is commonly referred to as a powerful antioxidant, but the current results showed that EGCG can also act as an antioxidant in some cases [44]. In different stages of an experimental lung cancer, EGCG and theaflavins have been proven to reduce the proliferation index in a benzo(a)pyrene[B(a)P]-induced lung carcinogenesis mouse model. When used theaflavins in 0.02 mg/mouse/day and EGCG dose of 0.01 mg/mouse/day, results show that both of them reduced the obvious carcinoma and dysplasia in situ at 8th, 17th, and 26th weeks. In Swiss albino rats, GTP treatment and black tea polyphenols (BTP) at dosage of 0.1 and 0.2% resulted in low incidence of diethylnitrosamine-induced alveologenic tumors, which resulted in the inhibition of the expression of lung cancer caused by Akt, cyclooxygenase (COX)-2, and nuclear factor kappa-B (NF-κB) [45]. The combination of liquid Polyphenon E (0.25 or 0.25%) and atorvastatin-inhibited lung cancer induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) in mice. Low-dose combination of Polyphenon E and atorvastatin significantly reduced the lung tumor diversity and enhanced cell apoptosis but inhibited tumor burden at myelogenous leukemia 1 (Mcl-1) level. Results show that lung tumors were effectively inhibited by atorvastatin and Polyphenon E, and *in vitro* and *in vivo*, the action between the two agents was synergistic. The inhibition activity of atomized difluoromethylornithine (DFMO) and Polyphenon E (1% wt/wt diet) administration was investigated in A/J mice injected with B(a)P. Polyphenon E did not suppress tumor treatment on average diversity but decreased the animal tumor load and significantly reduced the largest carcinoma [46].

3.2. Isothiocyanates and lung cancer

Isothiocyanates (ITCs) existed in cruciferous vegetables, which are converted into glucose and ITC by the enzyme myrosinase. Benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), and sulforaphane are widely studied for their chemopreventive and anticancer effects [47]. Recently, BITC-inhibited gefitinib-resistant human NSCLC growth, induction of apoptosis, caspase-3 activation, cell-cycle arrest in G2/M phase, ROS generation, glutathione depletion, inhibition of protein kinase activity, NF-κB transcription activation, and activation of mitogen-activated protein kinase (MAPK) and activating protein (AP)-1. PEITC declined the first phase of enzymes involved in the activation of several carcinogenic substances. PEITC also activated the second phase of enzyme activity, which is responsible for many carcinogenic metabolism and oxidative stresses. Isothiocyanates are proven to demonstrate anticancer behavior by inducing apoptosis and inhibition of the cell-cycle stage.

Some reports showed that several mechanisms have been postulated to determine the ITC against the mechanism of lung cancer. Importantly, researchers thought that tubulin is one of the targets in the body for ITC binding and covalent binding of BITC, PEITC, sulforaphane tubulin. Binding with cell apoptosis induced the cell ability and mitosis arrest [48]. The effect of oral sulforaphane (9 μmol/mouse/day) in reducing the oxidative damage caused by B(a)P (100 mg/kg body weight, i.p.) in Swiss albino rats was determined. Oral sulforaphane reduced hydrogen peroxide production, increased the release of mitochondrial cytochrome c, and reduced the expression of Bcl2, Bax, and caspase-3. Newborn mice were exposed to cigarette smoke for 120 consecutive days, beginning at birth, as well as to budesonide in diet (2.4 mg/kg in diet) and PEITC (1000 mg/kg in diet) and N-acetylcysteine in drinking water (1000 mg/kg) of oral drugs, until 210 days. High incidence of benign lung tumor multiplicity and an increase in pulmonary malignant tumor exposure to cigarette smoke and budesonide were observed in the carcinogenicity of PEITC and NAC treatment of mice lung exposed to cigarette smoke. Budesonide, PEITC, and NAC treatments reduced the yield of cigarette mainstream smoke, which induced lung benign or malignant tumor, showing mirror smokers' intervention in the experimental situation. As compared with the NNK-treated control group, Conaway et al. investigated the influence of sulforaphane, PEITC, and NAC yoke compound progress/J mice lung adenoma and adenocarcinoma [49] by reducing the incidence of adenocarcinoma PEITC in treated group of 3 and 1.5 mmol/kg each diet and PEITC-NAC, which used in 8 and 4 mmol/kg each diet in treatment group. Low incidence of lung cancer was showed in the treatment of sulforaphane-NAC (8 and 4 mmol/kg diet) in the diet. The results show that sulforaphane, and NAC yoke, and PEITC compound reducing cell proliferation and inducing apoptosis in tobacco carcinogen-treated A/J mice and resulting in inhibited the progress of adenocarcinoma in lung adenoma [27]. The influence of PEITC diet (3 μmol/g diet) and BITC (1 μmol/g diet) and a mixture of BITC + PEITC (1 and 3 μmol/g diet) on hemoglobin (Hb) adducts of B(a)P and DNA and NNK and two urinary metabolites are worthy of investigation. In urine, NNAL-Gluc and 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) were measured. After 2 and 4 months, a significant reduction in the level of 4-hydroxy-1-(3-pyridyl)-1-butanone releasing DNA adducts of the NNK lung was caused by BITC + PEITC or PEITC,

whereas no effect was demonstrated by BITC. From 2 weeks to 12 weeks, BITC + PEITC or PEITC also inhibited the Hb adduct of NNK and showed no effect on B(a)P adduct. A significant increase in the NNK level was also observed in rats after treatment with NNAL and NNAL-Gluc PEITC, as well as with PEITC or BITC + PEITC [50]. These findings suggest that PEITC or BITC + PEITC Hb released the DNA adduct formation in the lungs of mice that received B(a)P + nitrosamines. However, the BITC adduct was not influenced by B(a)P or nitrosamines. Before each of the three carcinogenic polycyclic aromatic hydrocarbons (PAHs) were found in cigarettes, treatment with BITC (6.7 and 13.4 μmol) was performed: B(a)P, 5-methylchrysene (5-MeC), and dibenz[a,h] anthracene [DBahA]; Compared with beta hydroxyl acid (BHA) and sulforaphane, these PAHs more effectively inhibited lung tumor multiplicity [51].

3.3. Indole-3-carbinol and lung cancer

An autolysis product of glucosinolate has been reported to exert anticancer effects; this product is indole-3-carbinol (I3C), which is present in Brassica plants like cabbage, cauliflower kale, broccoli, and Brussels sprouts [52].

After the postinitiation or progression protocol in A/J mice, we assessed how I3C inhibited tobacco carcinogen–induced lung adenocarcinoma. After treatment with I3C during the postinitiation period, reduction was observed in the tumor multiplicity, hyperplastic foci, adenoma, adenoma with dysplasia, and adenocarcinoma. When I3C was given during tumor progression, an increase was observed in the multiplicities of smaller tumors and decrease in larger tumors. I3C was found to efficiently inhibit the development of pulmonary adenocarcinoma. Moreover, via modulation of the phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway, the anticancer effects of I3C were mediated [53]. Silibinin used in 7 μmol/g/diet and I3C used in 10 μmol/g each diet reduced the multiplicities of tumors on the adenocarcinoma and surface of the lung in NNK-treated mice. Additionally, as compared with I3C or silibinin alone, I3C and silibinin were strongly affect cyclin D1 and poly (ADP-ribose) polymerase (PARP), p-Akt, p-ERK cleavage expression levels. Thus, against the development of lung cancer in A/J mice, this study proved that the findings of the combined treatment of silibinin and I3C afforded more protection and can be used to prevent cancer in current and former smokers [54]. Investigation of this effect showed that I3C (100 or 150 μM) on vinyl carbamate (VC) induced deregulation of microRNA (miRNA) levels in lung tissues of female A/J mice. Compared with mice treated with VC alone, the miR-21, mir-31, miR-130a, miR-146b, and miR-377 expression levels decreased in mice treated with VC and I3C in their diet. The development of lung cancer showed a significant relationship with abnormal miRNA expression. In lung tumors, compared with normal lungs, the results explained distinctive changes in the expression of several miRNAs. I3C exerted effects on most of the miRNAs. Myo-inositol (MI; 56 μmol/g/diet) and I3C (30 or 70 μmol/g/diet) against VC-induced lung cancer were applied. With higher dose on the lung surface, incidence of cancer, multiplicity, size, and adenoma with cellular pleomorphism, the lower dose of I3C showed fewer effects, whereas the higher dose of I3C decreased the multiplicities of tumors on treatment of mice. IκBα degradation, NF-κB activation, COX-2,

p-Akt, and activation of caspase-3 and PARP cleavage were inhibited by treatment with higher dose of I3C [55].

3.4. Genistein and lung cancer

The most abundant isoflavone in soybean, genistein (4,5,7-trihydroxyisoflavone), has been widely reported for its chemotherapeutic and chemopreventive effects. Recently, lung tumor growth was suppressed *in vivo* in a dose-dependent manner and apparently showed no toxicity on a derivative of genistein, 7-difluoromethyl-5,4′-dimethoxygenistein [56]. A significant decrease in tumor growth was found in a xenograft model for treatment of mice with a combination of gefitinib and genistein [57]. During the phase of pneumonitis, in rats receiving genistein (750 mg/kg body weight), the increase of breathing rate was inhibited after irradiation with 18 Gy at approximately 0.5 Gy/min and a delay of 50–80 days in Sprague-Dawley rats. After irradiation for 28 weeks and treatment with genistein, TNF-α, IL-1β, TGF-β, and collagen also decreased. The levels of 8-OHdG content also decreased, and the protection against DNA damage was measured in surviving rats. Treatment with genistein after irradiation indicated that DNA damage is caused by the production of ROS, which also reduced DNA damage in the form of micronuclear formation [57].

For lung metastasis induced by B16F-10 melanoma cells in C57BL/6 mice, the inhibition effects of dietary soybean isoflavones, genistein, and daidzein were investigated. Compared with untreated tumor-bearing animals, treatment with genistein (200 μmol/kg body weight) caused lung tumor nodule formation inhibition, and the lung collagen hydroxyproline content and serum sialic acid level were inhibited. The life span of the tumor-bearing animals was also increased by treatment with genistein [58].

3.5. Curcumin and lung cancer

Curcumin (diferuloylmethane) is derived from the plant *C. longa*. The antiangiogenic, analgesic, antioxidant, anti-inflammatory, and antiseptic properties of curcumin have been widely studied [59].

Experiments showed that curcumin (0.6%) can decrease the expression of COX2 in subcutaneous tumor *in vivo* and the weight of intralung tumors but can increase the survival rate. Curcumin also increased the survival of athymic nude mice and inhibited the tumor growth of orthotopic human NSCLC xenografts [60]. Curcumin and erlotinib significantly inhibited tumor growth of erlotinib-resistant NSCLC cells *in vivo* compared with the control, and this finding suggested that during treatment with erlotinib, curcumin might be a prospective adjuvant for NSCLC patients. The growth of human lung cancer xenografts in nude mice was inhibited by oral intake of curcumin (500 mg/kg/body/day) and phosphosulindac (200 mg/kg/day); curcumin may improve the phosphosulindac bioavailability and inhibition of efflux transporters [61]. Curcumin (50-mg/kg body weight) was found to increase cell survival, which contributed to T-cell–mediated adaptive immune response and decrease in tumor growth. Low-dose curcumin increased T cells derived from 3LL-tumor-bearing mice,

particularly $CD8^+$ T cells, but high-dose curcumin (100-mg/kg body weight) decreased T cells which exhibited the enhancement of cytotoxicity and interferon-γ (IFN-γ) secretion and proliferation against 3LL tumor cells. In lung-tumor-bearing models, the results pointed out that curcumin may support the immune system and induce antitumor immune response via the T-cell-mediated effect. Cancer treatment by curcumin can prove it as an immunologically safe drug. These data provide further evidence that curcumin can play a role in lung cancer therapy [62].

3.6. Fisetin and lung cancer

Fisetin (3,3′,4′,7-tetrahydroxyflavone) is found in strawberry, persimmon, grape, apple, cucumber, and onion. It is a naturally occurring flavonoid with apoptotic and antiangiogenic properties, as well as antiproliferative effects in cancer cells [63].

A previously published study showed that treatment with fisetin (25-mg/kg body weight) decreased histological lesions and lipid peroxidation levels and modulated the enzymatic and nonenzymatic antioxidants in B(a)P-treated Swiss albino mice [64]. In LLC-bearing mice, Matrigel plug assay showed that when fisetin was treated with dose of 223 mg/kg inhibited angiogenesis. Tumor growth was also inhibited by fisetin, which is similar to the effect of low-dose cyclophosphamide (30-mg/kg body weight). Combination of fisetin and cyclophosphamide led to the striking improvement in antitumor activity and decrease in microvessel density and low systemic toxicity. Fisetin exhibited anticancer activities and antiangiogenic properties in LLC-bearing mice.

3.7. Pomegranate polyphenols and lung cancer

Pomegranate (*Punica granatum*, Punicaceae) was cultivated in Afghanistan, India, China, Japan, Russia, and the United States. It is an edible fruit widely comprising about 80% juice and 20% seed.

Pomegranate can provide oral administration of pomegranate fruit extract (PFE), which caused tumor growth inhibition in athymic nude mice implanted with human lung cancer A549 cells. Pomegranate can induce the appearance of small solid tumors, which prolonged survival time in animal models [65]. B(a)P and N-nitroso-tris-chloroethylurea (NTCU) in A/J mice were investigated, caused of effects of oral consumption of a human-achievable dose of PFE dose of 0.2%, w/v effect on progression, angiogenesis, growth, and signaling pathways in two models of lung cancer. For treatment with PFE and B(a)P or NTCU, we found little lung tumor multiplicities of tumor incidence in mice. Oral administration of PFE caused inhibition of NF-κB, MAPK, and PI3K, as well as phosphorylation of Akt, mammalian target of rapamycin (mTOR), c-met, and lung markers that inhibited B(a)P- and NTCU-treated mice; cell proliferation and angiogenesis were also inhibited. By targeting multiple signaling pathways and associated events, PFE demonstrated activity against lung cancer, and these events are critical for the development and progression of lung carcinoma [66]. Molecular targets of antilung cancer natural product molecules in the body were shown in **Table 1**.

Active natural products for antilung cancer	Molecular targets					
Green tea	MAPK	mTOR	EGFR	p53	PKC	TGF-β
Isothiocyanates	MAPK	AP-1	NF-κB	Akt	Nrf2	Keap1
Genistein	EGFR	PGE2	Akt	NF-κB	Cox-2	TNF-α
Pomegranate	PI3K	Akt	mTOR	MAPK	c-met	NF-κB
Fisetin	Akt	mTOR	PI3K	AMPKα	AP-1	NF-κB
Curcumin	Wnt/β-catenin	Cox-2	NF-κB	EGFR	STAT-3	Survivin
Indole-3-carbinol	IL-6	IL-1β	p53	PI3K	Akt	Cox-2

Table 1. Antilung cancer natural product molecules in the body and molecular targets.

4. Natural product molecules for the treatment of lung cancer in clinical trials

Complementary and alternative medicine (CAM), including natural product molecules, increased survival in cancer patients [67]. Recently, 453 cancer patients in a cohort study showed that 77% of patients use herbal medicines combined with conventional treatment to reduce the therapy-associated toxicity and cancer-related symptoms, improve the immune system, and even eliminate cancer directly [68].

Conventional chemotherapy is combined with natural product molecules to increase the therapeutic effect and QoL. Sixty-three in-patients diagnosed with IV NSCLC and stage IIIb were treated as randomized-controlled trial, Gujin granules (Jiangyin Tianjiang Pharmaceutical Co., China) and Shengmai injection (Ya'an Sanjiu Pharmaceutical Co., China) were administered intravenously and orally. Navelbine and cisplatin (NP) chemotherapy were treated in all the groups. This combination therapy enhanced median survival time (P = 0.014) and response rate to 48.5% (16/33) compared to untreated control (32.2% = 9/28) in the control group (P = 0.0373). However, herbal medicine did not affect the bone marrow inhibition occurrence, median time to progression, 1-year survival rate, and mean cycles of chemotherapy applied. Among 232 NSCLC patients, by using the QoL scale of the European Organization for Research on Treatment of Cancer (QLQ-C30) (Lin and Li, 2007), treated with Shenqi-fuzheng injection (Lizhu Co., China), improved QoL and the response rate. In another trail, Yiqi Yangyin Jiedu Decoction significantly increased the immunological parameters and Karnofsky (KPS) score, including $CD4^+$, $CD4^+/CD8^+$, $CD3^+$, and $CD8^+/CD28^+$, and all the patients were treated with NP or gemcitabine and cisplatin (GP) compared with the untreated control [69].

Natural product molecules can improve the QoL of patients with lung cancer. Recently, QoL is improved in NSCLC patients with long-term prognostic factors of survival. In a RCT and herbal Feiji recipe, Feiji was found to improve the clinical therapeutic effect, reduce the side effects of chemotherapy before this research by adding higher scores in the role, as well as the social and economic status ($P < 0.05$ or $P < 0.01$) based on the QLQ C30 questionnaire. Similarly,

in a clinical trial of 294 patients with advanced NSCLC and treated with Shenfu injection of traditional Chinese medicine, on the basis of the functional assessment of cancer therapy-lung (FACT-L), Chinese medicine positively affected health when used alone, as well as with emotional, functional, and additional care when performing traditional chemotherapy ($P < 0.05$) [70].

The negative influence of natural product molecules is shown by traditional intervention. One of the main risks of conventional treatment is pneumonia in patients with lung cancer, and this complication may be caused by radiation therapy intervention and symptoms of severe dyspnea, cough, fever, respiratory failure and/or verticillium wilt in severe cases. With Dixiong soup in clinical trials of 46 NSCLC patients who underwent radiotherapy, based on the incidence of pneumonia after radiotherapy and QoL using continued to shrink the clinical imaging physical difficulty breathing (CRP) score, tumor radiotherapy group (RTOG) rating scores, and KPS score, Dixiong Shang Xianzhu reduced the incidence of radioactive pneumonia (treatment, 10.0%; control, 26.3%; $P = 0.0032$) and improved the continued decline of CRP dyspnea score, RTOG classification score ($P < 0.05$), and KPS score ($P < 0.01$). Similarly, substantial evidence demonstrated good effect of herbal Liangxue jiedu huoxue soup, Qingjin runfei decoction, and Shenqi fuzheng injection. Hydrochloric acid, stand for kang, topoisomerase inhibitors, and Chinese tree *Camptotheca acuminata* (Cornaceae) are used for lung cancer treatment combined with other conventional drugs, in spite of the side effects including leukopenia and diarrhea. With Hangeshash into RCTs, 44 irinotecan-treated NSCLC patients showed that TJ-14 can significantly improve the grade ($P = 0.044$) and frequency of diarrhea to grades 3 and 4 ($P = 0.018$). A list of therapeutic approaches and outcome assessment and the quality of herbal medication were listed in **Table 2** [71].

CHM formula	No. of participants/ dropout or withdrawal	TNM stage	Control group intervention	Assessment of outcome	Duration (week)	Jadad scale
Shengmai injection Gujin grand decoction	106/6 dropout patients	IIIB–IV	NP	Tumor response, survival rate, chemotoxicity	12	3
Feiji recipe	77/0	IIIB–IV	NP/TP	Tumor response, survival rate, CD62P	8	3
Yinqi Yangyin decoction	60/3 withdrawals	IIIB–IV	GP	Tumor response, survival rate, chemotoxicity, KPS	8	3
Fuzheng Kangai decoction	129/drop out: 5 patients in CTC and 4 patients in CT; withdraw: 2 patients in CTC and 3 patients in CT	IIIB–IV	MVP combined with radiotherapy	Tumor response, chemotoxicity, KPS	12	3
Shengmai injection	60/0	IIB–IV	DP	Tumor response, chemotoxicity	8	3

Table 2. Therapeutic approaches and outcome assessment of herbal medication.

5. Constraints and current clinical trials and the challenges of natural product molecules

The traditional Chinese medicine (TCM) clinical research also presents some limitations and difficulties. As mentioned in a recent review, TCM, including herbal medicine, establishes its unique features, such as holism and personalization. According to the theory of traditional Chinese medicine, a patient is diagnosed with symptoms rather than the disease itself and prescribed with a personalized herbal formula to treat the symptoms. Although RCT is a powerful tool to verify the clinical curative effect of health care, a RCT on the application of personalized herbs remains a challenge because of heterogeneous batch management. Likewise, Chinese medicine intervention heterogeneity leads to some difficulties for high-performance analysis of natural product molecules. Therefore, for cancer research in the future, particularly on herbs and plant chemicals, we suggest that the quality control should be performed consistently with batch and pharmacokinetic studies on TCM and its components, which perform antitumor activities in lung cancer.

There still exist some problems to standardize in the use of natural products in prevention or treatment lung cancer. First, the purity of traditional Chinese medicine is not high, most of the traditional Chinese medicine preparations from to the original drug, powder, or crude extract, so it works slowly. Second, inconvenient to use, taking traditional Chinese medicine generally to a large package of herbs, and not easy to drink because of bitterness. Third, the dose of natural products is difficult to grasp, and the available activity contents are different due to the different plants.

As a result, the problems should be specified to herbs in the QoL in a sense, and the therapeutic effect may vary among different batches. Furthermore, the lack of rigorous methods, risk of possible bias, and a relatively small number of patients involved were repeatedly pointed out in the previous literature on herbal application in lung cancer patients.

However, the most recent basic and clinical research showed a growing body of evidence to support the notion indicating that herbs may be beneficial and effective in the treatment and improvement of the QoL of patients with lung cancer, as well as prevent the side effects of conventional therapy and improve the immune parameters. However, researchers must develop novel specific methods to completely solve the challenges of the present study and verify the credibility of possible herbs.

Despite the great progress of lung cancer treatment, lung cancer remains a leading cause of cancer death worldwide. Molecule-targeted therapy has recently attracted research attention; for example, the treatment of tyrosine kinase inhibitors and erlotinib for epidermal growth factor receptor (EGFR) and its downstream mTOR signaling factors and bevacizumab, as well as humanized monoclonal antibody, can bind to VEGF to increase the response rate and progression-free survival (PFS) of patients on treatment with carboplatin, paclitaxel, cisplatin, and gemcitabine in phase II trials. Plenty of evidence from a previous study showed that the eastern medicine herbal therapy is effective in lung cancer treatment by regulating cell proliferation, apoptosis, angiogenesis, and metastasis in multidrug-resistant tuberculosis patients. These activities can participate in a biological process of target molecule toxicity to normalize

lung epithelial cells in lung cancer. Although various herbal formulas and plants are traditionally used to treat lung diseases since the ancient times, the folk prescription of lung cancer guidelines and standards is the first published by the American College of Chest Physicians including complementary and alternative medicine in 2007, as well as the systematic review of the potential of herbs and its active compounds in lung cancer treatment without execution. In the current review, we recommend the potential of herbs and plant chemicals, which are commonly used for the treatment of lung diseases, including cancer, for folk prescription of critical data analysis and discussion *in vitro* or *in vivo* laboratory experimental models and clinical trials. Overall, we conclude that herbs and plant chemicals are potentially effective anticancer drugs for the treatment and prevention of lung cancer by adjusting the multimolecular targets involved in angiogenesis, metastasis, and serious side effects, thereby providing only quality control and reproducibility of problem solving.

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