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Review Article
Therapeutic Potential of Natural Products in Lung Cancer

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Abstract

Lung cancer is the leading cause of all cancer morbidity and mortality worldwide. Owing to the paucity of effective diagnostic and treatment strategies, new drugs or strategies must be found and developed for the treatment of lung cancer. Natural products (NPs) have excellent properties for the treatment of cancer, including lung cancer and are the most productive source of inspiration for discovery of new drug leads. NPs inhibit the progression of cancer by suppressing cancer cell proliferation, migration and invasion, inducing cell apoptosis and enhancing the effect of antitumour drugs. Therefore, the use of NPs may be a promising strategy for treatment of lung cancer owing to their excellent properties and few side effects. In this review, the mechanisms of NPs in lung cancer to provide a new insight into the cure and the development of novel drugs for treating lung cancer was discussed.

Key words: Natural products, lung cancer, signalling pathway, mechanism

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INTRODUCTION

Lung cancer, which accounts for approximately 25% of all cancer deaths globally, is the primary cause of cancer morbidity and mortality worldwide, with an estimated 2 million new cases each year[1,2]. Lung cancer mainly falls into two categories: Non Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC) and NSCLC is the most frequent pathological type, occurring in 83% of all lung cancers[3]. Owing to the paucity of effective diagnostic and treatment strategies, the prognosis of lung cancer is poor with a 5 year relative survival rate of 19%[1]. To date, targeted therapy, radiotherapy and chemotherapy have been the most common methods for lung cancer therapy[4]. Although significant progress has been made in the treatment of lung cancer, there are still many challenges, such as drug resistance and undesirable side effects[5]. Therefore, it is necessary to find and develop new drugs or strategies for treating lung cancer.

In the past few decades, natural products (NPs), which have been confirmed to possess potent biological activity, have been the most productive source of inspiration for the discovery of new drug leads[6,7]. Approximately, one-third of small-molecule drugs introduced over the past four decades have been NPs or NP-derived compounds[6]. Extensive studies have demonstrated that NPs have excellent properties in the treatment of cancer, including lung cancer, gastric cancer and breast cancer[8]. These NPs inhibit the development of lung cancer by suppressing cancer cell proliferation, invasion and migration, as well as inducing apoptosis of lung cancer cells through multiple signalling molecules and pathways[9]. Herein, the mechanisms of NPs in lung cancer to provide a reference for the treatment and development of new drugs for treating lung cancer was discussed.

PURE NATURAL PRODUCTS IN LUNG CANCER

Natural compounds, including alkaloids, flavonoids, polyphenols, terpenoids, quinones, saponins and lignans, exhibit excellent antitumor activity. These compounds may provide preventive or adjuvant therapeutic approaches for lung cancer, indicating the significant potential role of natural compounds to treat lung cancer.

Alkaloids: Alkaloids are a class of nitrogenous organic compounds. Many studies have revealed that alkaloids possess potent anti-lung cancer properties (Refer to Fig. 1 for structures)[10]. For example, cytisine, a quinolizidine alkaloid, isolated from *Papilionaceae* and *Caesalpinioideae*, inhibited proliferation, induced apoptosis and arrested the cell cycle in the G2/M phase of A549 cells. Mechanistically, cytisine induced cell apoptosis by upregulating the expression of B-cell lymphoma 2 (Bcl-2)-associated death promoter (BAD), cleaved caspase-3 and cleaved-polymerase (PARP) and down regulating the expression of Bcl-2, pro-caspase-3 and pro-PARP through the mitogen-activated protein kinase/signal transducer and activator of transcription 3/nuclear factor-κB (MAPK/STAT3/NF-κB) signalling pathway. Moreover, cytisine arrested the cell cycle in the G2/M phase via the protein kinase B (AKT)signalling pathway[11]. Daurisoline is a bis-benzylisoquinoline alkaloid that was isolated from *Rhizoma menispermi*. Daurisoline induced G1 phase arrest by targeting heat shock protein 90 (HSP90) to disrupt the interaction between HSP90 and β-catenin and down regulate the expression of the cellular myelocytomatosis oncogene (c-myc) and cyclin D1 in A549 and Hop62 cells[12]. Sinomenine inhibited hexokinase II-mediated aerobic glycolysis, thus initiating apoptosis and reducing cell viability in HCC827, H1975 and H460 cells. Sinomenine was also found to retard tumour growth in HCC827 and H1975 xenograft nude mice[13]. Lycorine is an isoquinoline alkaloid that was reported to inhibit proliferation and induce apoptosis in A549 and H1299 cells by regulating the miR-186/cyclin dependent kinase 1 (CDK1) axis[14]; this study demonstrated that lycorine could affect the proliferation and apoptosis of lung cancer cells by altering the expression of microRNAs. Oxymatrine (OMT) suppresses the constitutive activation of signal transducer and activator of transcription 5 (STAT5) by inhibiting the activation of the cellular sarcoma gene (c-Src) and Janus-activated kinase 1/2 (JAK1/2), nuclear localization and STAT5 binding to DNA in A549 cells, indicating that oxymatrine exerts its anticancer effects by deactivating STAT5 signalling[15]. Krukovine is a bisbenzylisoquinoline alkaloid that is isolated from the bark of *Abuta grandifolia* (Mart.) Sandw. Krukovine induced apoptosis, inhibited cell colony formation and arrested the cell cycle in the G1 phase by suppressing the RAF/ERK pathway and AKT signalling in H460 and A549 cells[16]. Coptisine, which was isolated from the seeds of *Fumaria indica*, induced the apoptosis of A549 cells, as evidenced by the activation of caspase 3, caspase 8 and caspase 9 and cleavage of polyadenosine diphosphate ribose polymerase. In addition, coptisine could cause DNA damage, increase Reactive Oxygen Species (ROS) generation and arrest cell cycle in the G2/M phase by inhibiting the expression of cyclin B1, cell division cycle protein 2 (CDC2) and CDC25c and upregulating p21 expression[17]. 11-methoxytabersonine (11-MT) is an aspidosperma-type alkaloid isolated from

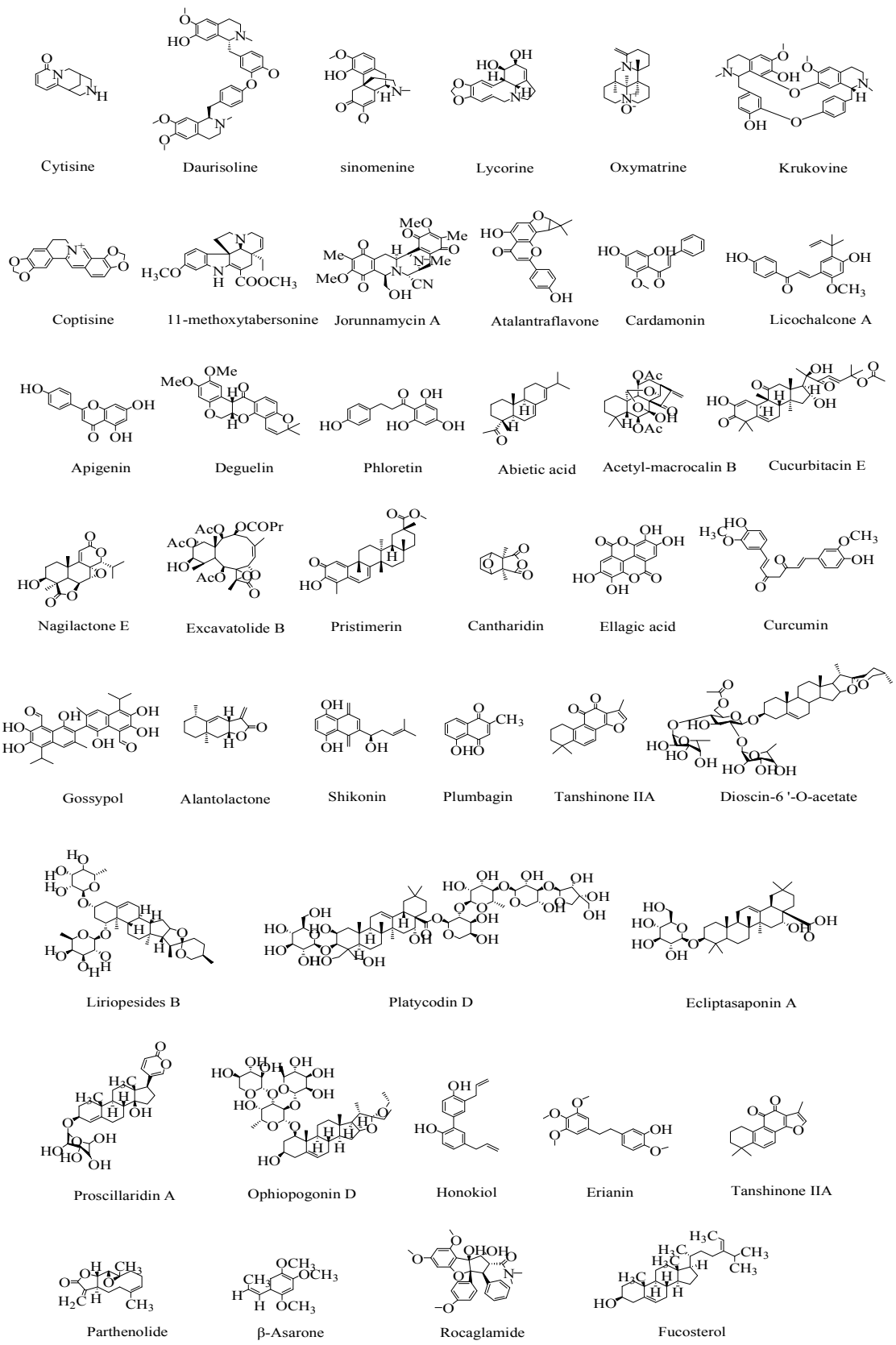

Fig. 1: Chemical structures of main natural compounds for the treatment of lung cancer

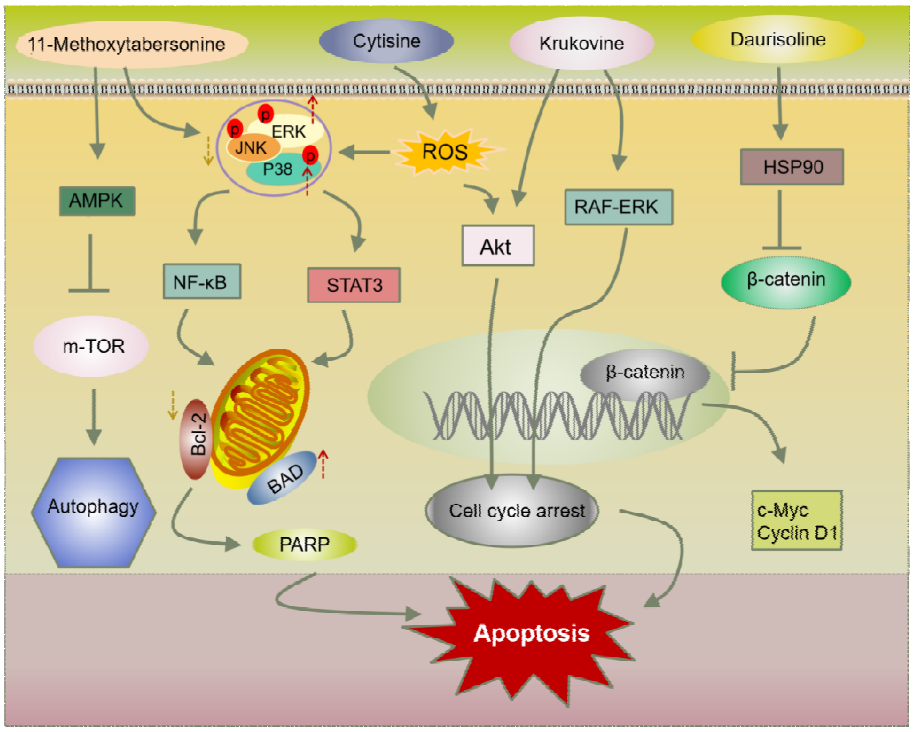

Fig. 2: Mechanisms of main alkaloids on lung cancer

Cytisine induced apoptosis through MAPK/STAT3/NF-κB signaling pathway and inhibited proliferation via AKT signaling pathway. Krukovine induced apoptosis and suppressed proliferation via RAF-ERK pathway and AKT signaling. Daurisoline induced cell cycle arrest by targeting HSP90 to disrupt the interaction between HSP90 and β-catenin and down regulating the expression of c-myc and cyclin D1. 11-methoxytabersonine inhibited AMPK-mTOR signaling pathway and the phosphorylation of JNK to induce autophagy

Tabernaemontana bovina. It was reported that 11-MT inhibited the AMPK-mTOR signalling pathway and the phosphorylation of c-Jun N-terminal kinase (JNK), which in turn induced autophagy in A549 and H157 cells[18], suggesting that 11-MT could inhibit the development of lung cancer by inducing autophagy. Jorunnamycin A significantly suppressed metastasis by inhibiting epithelial to mesenchymal transition (EMT), sensitizing H460 cells to anoikis and repressing anchorage-independent survival[19]. Collectively, these studies indicated that alkaloids show excellent activities for inhibiting lung cancer by affecting their respective targets (Fig. 2), suggesting that alkaloids might act as novel drugs in the therapy of lung cancer.

Flavonoids: Flavonoids are one of the largest classes of secondary metabolites that are toxic to cancer cells but not harmful to normal cells[20,21]. It has been reported that some flavonoids, including atalantraflavone (AFL), cardamonin, licochalcone A (lico A), apigenin (APG),deguelin and phloretin possess potent activity against lung cancer (Refer to Fig. 1 for structures)[22-27]. AFL is isolated from *Atalantia monophylla* (L.) and markedly inhibited cell viability and colony formation and initiated apoptosis of A549 cells by destabilizing Twist-related protein 1 (Twist1). Moreover, overexpression of Twist1 significantly reversed the anticancer effect of AFL. In addition, AFL sensitized A549 cells to cisplatin (DDP) treatment and repressed the proliferation and metastasis of A549 cells[22], suggesting that AFL could sensitize lung cancer cells to antitumour drugs. Cardamonin, which is isolated from *Alpinia katsumadai* Hayata, is a chalcone that significantly inhibits migration, invasion and EMT inA549 and H460 cells. Furthermore, cardamonin induced apoptosis and G2/M phase arrest by down regulating the expression of p-Akt, p-mammalian target of rapamycin (p-mTOR) and the phosphorylation levels of phosphatidylinositol 3-kinase (PI3K), indicating that the PI3K/Akt/mTOR pathway might contribute to the response of lung cancer cells to cardamonin[23]. Lico A can upregulate miR-144-3p by reducing the expression of nuclear factor E2-related factor (Nrf2) to initiate apoptosis and autophagy in H292 cells[24]. APG inhibited the proliferation, migration and invasion of A549 cells by upregulating the level of Akt and modulating the expression of its downstream genes, such as matrix metalloproteinases-2 (MMP-2), MMP-9, glycogen synthase kinase-3β (GSK3β) and human enhancer of

filamentation 1 (HEF1)[25]. Deguelin is a rotenoid isolated from *Derris trifoliata* Lour that suppresses the migration and invasion of NCI-H23, NCI-H1299 and A549 cells by inhibiting the expression of Cathepsin Z (CtsZ) and the activation of focal adhesion kinase/Src/Paxillin (FAK/Src/PXN)signalling and disturbing the interaction of CtsZ with integrin β3[26]. Deguelin could simultaneously inhibit the progression of NSCLC by promoting GSK3β/F-box and WD repeat domain-containing protein 7(FBW7)-mediated myeloid cell leukaemia sequence 1 (Mcl-1) destabilization and suppressing Epidermal Growth Factor Receptor (EGFR) signalling[28]. Phloretin inhibited the proliferation, initiated apoptosis in A549 cells and enhanced the anticancer effect of DDP by inhibiting the expression of Bcl-2, elevating the levels of cleaved-caspase-3 and -9 and deregulating MMP-2 and -9 at both the protein and gene levels[27]. Taken together, flavonoids are a class of natural compounds that exhibit remarkable anticancer properties and might be promising candidates for the discovery of new anti-lung cancer drug leads.

Terpenoids: Terpenoids, consisting of a plurality of hydrocarbon isoprene (C_5) structural units and their oxygenated derivatives, are wide spread in the plant kingdom[29]. Relevant investigations indicated that terpenoids show notable effects against lung cancer (Refer to Fig. 1 for structures). For instance, Abietic Acid (AA) inhibited the growth of PC-9 and H1975 cells by targeting IκB kinaseβ (IKKβ) and suppressing the phosphorylation of IKKβ and inhibitor κB (IκB), which resulted in the nuclear translocation of NF-κB[30]. Acetyl-macrocalin B (A-macB), isolated from *Isodon sylvatica*, induced apoptosis by activating p38 MAPK, which modulated the caspase-9-dependent intrinsic apoptotic pathway. Meanwhile, A-macB arrested the cell cycle in the G2/M phase through the Chk1/2-CDC25c-CDC2/cyclin B axis, as indicated by checkpoint kinase 1/2(Chk1/2) activation and the degradation of CDC25c,which led to the inactivation of the CDC2/cyclin B1 complex and CDC2 phosphorylation[31]. Cucurbitacin E (CuE) upregulated the expression of Bax and the caspase family and decreased the levels of Bcl-2 and Bcl-xL, which in turn induced apoptosis of 95D cells. In addition, CuE resulted in ROS-mediated autophagy via the AKT/mTOR signalling pathway[32]. Nagilactone E (NLE) could reduce the level of cyclin B1 to induce the cell cycle in G2/M phase arrest of A549 and NCI-H1975 cells[33]. Excavatolide B (Exc.B) effectively suppressed the proliferation of A549 cells by upregulating phosphatase and tensin homologue (PTEN) expression, reducing the levels of p-AKT and NF-κB and modulating the expression of peroxisome proliferator activated receptor γ[34]. Pristimerin, isolated from *Celastrus aculeatus* Merr, decreased sonic hedgehog (Shh)-mediated nuclear distribution of glioma associated oncogene 1 (Gli1) and blocked the phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR2), Akt and extracellular signal-regulated kinase (ERK) and these effects resulted in the inhibition of angiogenesis and tumour growth in NCI-H1299 xenograft mice[35]. Cantharidin (CTD) suppressed the expression of urokinase plasminogen activator (UPA) and MAPK signalling pathways, which in turn suppressed the migration and invasion of lung cancer cells[36].

Polyphenols: Polyphenols, which have one or more aromatic rings, are considered to be one of the most promising classes of candidate drugs for the prevention and treatment of various malignant tumours, including lung cancer (Refer to Fig. 1 for structures)[37,38]. For example, Ellagic Acid (EA) significantly inhibited the proliferation of HOP62 and H1975 cells by repressing mitochondrial respiration (OCR) through hypoxia inducible factor-1α (HIF-1α) inactivation and AMP-activated protein kinase (AMPK) acivation[39]. Curcumin was reported to induce apoptosis and inhibit the proliferation of NCI-H292 cells by increasing the levels of suppressors of cytokine signalling proteins 1 (SOCS1) and SOCS3 and suppressed STAT3 activity, which led to an increase in forkhead box transcription factor A2 (FOXA2) expression[40]. Another study demonstrated that curcumin could suppress the viability of lung cancer stem cells by inactivating Shh and the Wnt/β catenin signalling pathway[41].Gossypol repressed proliferation and migration and initiated apoptosis by binding to the kinase domain of $EGFR^{L858R/T790M}$ in the H1975 cell line[42].

Quinones: Quinones are a class of NPs with unsaturated cyclo diketone structures that possess multiple biological activities, including anticancer, anti-inflammatory, antiviral properties (Refer to Fig. 1 for structures)[43]. Alantolactone, isolated from *Inula helenium* L., is a sesquiterpene lactone that can inhibit the progression of lung cancer NCI-H1299 and Anip973 cells by activating the p38 MAPK pathway and inhibiting the NF-κB pathway[44]. Shikonin significantly down regulated the PKM2/stat3/cyclinD1 signalling pathway, which in turn promoted the effect of gefitinib against A549 and H1299 cells[45], suggesting that shikonin could promote the therapeutic effect of anti lung cancer drugs. Plumbagin (PL), a naphthoquinone compound, is extracted from *Plumbago zeylanica* and reduces the viability of A549 and A549GR cell lines by inducing S-G2/M phase arrest and causes apoptosis by activating the

mitochondrial-mediated apoptotic pathway by promoting ROS production[46]. Tanshinone IIA (Tan IIA) inhibited the growth of NSCLC cells by suppressing the phosphorylation of EGFR, Akt and ERK1/2, reducing the expression of Bax and Bcl-2, while upregulating the expression of cleaved-PARP and -caspase 3[47].

Saponins: Saponins are a group of amphiphilic glycosides with triterpenoids or spirostanol as their glycosides, which exhibit remarkable antitumour biological activity (Refer to Fig. 1 for structures)[48]. Dioscin-6'-O-acetate (DA), a novel steroidal saponin, is extracted from *Dioscorea althaeoides* R. Knuth and was reported to induce apoptosis by decreasing the expression of p-PI3K, p-AKT and NF-κB p65 and the phosphorylation of ERK1/2, while promoting the expression of p-JNK and p-p38 in lung cancer H1299, H520 and H446 cell lines. In addition, DA markedly promoted ROS generation and caused cell cycle arrest at the S and sub G1 phases[49]. Liriopesides B (LPB) arrested the cell cycle in the G1/S phase in H460 and H1975 cells through the P21 cyclin D/CDK6 signalling pathway and initiated autophagy by decreasing expression of p mTOR and promoting the phosphorylation of AMPKα and unc-51-like autophagy-activating kinase 1 (ULK)[50]. Platycodin D(PD) decreased programmed death ligand-1(PD-L1), which is a critical immune checkpoint for cancer immunotherapy, at the protein level by promoting its release in NCI–H1975 cells[51].InH460 and H1975 cells, treatment with ecliptasaponin A(ES) induced autophagy and apoptosis by increasing the phosphorylation levels of apoptosis signal-regulating kinase 1 (ASK1) and JNK, which indicated that the ASK1/JNK signalling pathway might contribute to ES-induced apoptosis[52]. Proscillaridin A (PA) induced apoptosis by activating AMPK and JNK phosphorylation, upregulating DR4 expression and inhibiting ACC phosphorylation and the NF-κB signalling pathway. Further study *in vivo* showed that P.A suppressed tumour growth in H1975 xenograft nude mice[53]. Ophiopogonin D(OP-D) inhibited the activation of NF-κB, PI3K/AKT and activator protein-1 (AP-1), thus inhibiting the proliferation of H1299 cells and A549 cells[54].

Others: In addition to the common types of NPs, many other structural types of natural compounds also have anti-lung cancer effects (Refer to Fig. 1 for structures). Honokiol (HNK) is a natural lignan that is isolated from the bark of *Magnolia* trees and shows an extensive anticancer activity[55]. It was reported that HNK inhibited the growth and survival of KRAS mutant lung cancer cells by reducing the phosphorylation of c-RAF, ERK and AKT and induced autophagy by inhibiting mTOR phosphorylation. Additionally, honokiol may inhibit the progression of lung cancer by upregulating Sirt3 expression and decreasing the level of HIF-1α[56]. Moreover, HNK could also induce apoptosis by activating Endoplasmic Reticulum (ER) stress signalling pathway in A549 and 95-D cells[57]. Another study indicated that HNK suppressed lung cancer metastasis by inhibiting STAT3 phosphorylation[58]. A recent study demonstrated that erianin, a novel dibenzyl compound, inhibited proliferation and migration to against lung cancer H460 and H1299 cell lines by inducing ferroptosis through the calcium/calmodulin pathway[59]. Parthenolide (PTL) is a sesquiterpene lactone that reduces the phosphorylation of insulin-like growth factor 1 (IGF-1R), Akt and FoxO3α and these effects lead to the inhibition of the proliferation and migration of A549 cells[60]. Rocaglamide (RocA) promoted NK cell-mediated killing of NSCLC cells by inhibiting autophagy by decreasing the expression of unc-51 like autophagy activating kinase 1 (ULK1), revealing that RocA might be a promising candidate for cancer immunotherapy mediated by NK cells[61]. β-asarone repressed migration, invasion and adhesion, decreased viability and induced apoptosis of A549 cells by inhibiting the expression of p-GSK-3β, dishevelled 2 (DVL2), β-catenin, c-myc, cyclin D1 and MMP-7 through the Wnt/β-catenin signalling pathway[62]. Fucosterol is a phytosterol and was found to initiate apoptosis and cell cycle arrest of SK-LU-1 and A549 cells through the Raf/MEK/ERK signalling pathway[63].

In this section, all pure natural compounds that have significant properties in the treatment of lung cancer were discussed. Unfortunately, no connection was found between different types of compounds that are extensively scattered in every corner of nature. However, it was found that natural compounds possess obvious biological activities against lung cancer by targeting multiple pathways, which provides new strategies to find drug leads. Therefore, further *in vitro* and *in vivo* studies were required to elucidate the underlying mechanisms of NPs for the treatment of lung cancer. Hence, natural compounds have the potential to be used clinically in the future.

CRUDE EXTRACTS IN LUNG CANCER

Extraction of compounds from NPs is a productive source for discovery of new drug leads. Crude extracts can be administered and effectively quality controlled by extraction and separation. Recently, many crude extracts from medicinal plants have exhibited obvious anticancer properties. For instance, the ethanol extract of *Euphorbiaceae* (EE) significantly upregulated the levels of Bax and caspase 9 and

downregulated Bcl 2 expression, which induced the apoptosis of Lewis lung adenocarcinoma (LCC) cells. In addition, EEs caused cell cycle arrest in the G0/G1 phase in LCC cells, increased the activities of serum superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH Px) and inhibited tumour growth in tumour bearing mice[64]. *Melissa officinalis* L. ethanolic extract suppressed the growth of NCI-H460 cells by inducing apoptosis and cell cycle arrest, as evidenced by the reduction of pro-caspase 3 and upregulation of p53 expression[65].The extract of the roots of *Piper methysticum* suppressed norepinephrine(NE)-mediated intracellular calcium influx, which plays an essential role in the development and progression of lung cancer, by antagonizing β-adrenergic receptors (ARs) in H1299 cells[66]. *Cyclamen pseudibericum* (CP) petroleum ether and ethanol extract suppressed invasion and migration by targeting zinc-finger E-box binding homeobox 1 (ZEB1) through upregulating miR-200c by inhibiting EMT against lung cancer A549 cells[67]. This study indicated that ZEB1-mediated EMT might be associated with the antilung cancer effect of CP extract. Total ginsenoside extract (TGS) synergizes with mitomycin C (MMC) to inhibit the progression of lung cancer by suppressing Rad51-mediated DNA damage repair, by inhibiting the translocation of Rad51 from the cytoplasm to the nucleus and blocking the MMC-induced activation of p-MEK1/2 and p-ERK1/2 and the expression of Rad51[68]; this study revealed a novel treatment of lung cancer cells with TGS combined with MMC. The water extract of *P. koraiensis* pine cones induced apoptosis in A549, H1264, H1299 and Calu-6 cells by activating caspase-3, while polysaccharide (PGL) from *G. littoralis* could induce apoptosis by reducing the expression of Proliferating Cell Nuclear Antigen (PCNA)[69,70].

Although NPs have been confirmed to be an important source of drug discovery, it is not a good approach to try to find bioactive compounds from crude extracts of NPs due to the degradation of some effective active compounds under the high temperature. Meanwhile, the solvents may react with the effective ingredients. Moreover, the safety of the crude extracts of NPs is a critical problem. In the future, further studies are necessary to solve these problems.

TRADITIONAL CHINESE HERBAL FORMULAS IN LUNG CANCER

Traditional Chinese herbal formulas have a long history in the treatment of various diseases. Of note, many classic Chinese herbal formulas have been reported to show evident effects in the treatment of lung cancer. For example, Bu Fei Decoction (BFD) is a classic Chinese medicine formula that has been used for hundreds of years to nourishing the lungs. A recent study indicated that BFD exerted its anticancer effect by inhibiting the expression of apurinic/apyrimidinic endonuclease 1 (APE1) in H1975 and H292 cell lines[71]. Additionally, treatment with BFD significantly downregulated the expression of IL-10 and PD-L1 and thus inhibited the proliferation, invasion and migration of A549 and H1975 cells[72]. Maimendong and Qianjinweijing Tang (Jin formula), a well-known formula of traditional Chinese medicine for treating "Feiyong", inhibited the proliferation, migration and invasion and induced apoptosis of A549 and H1299 cells by targeting miR-149-3p by reducing the levels of β-catenin, c-myc and cyclin D1[73]. Miao-Yi-Ai-Tang (Miao) and XiaoaiJiedu recipe (XJR) exhibited the same effect of Jin formula by decreasing the expression of c-myc, AXIN and β-catenin and downregulating p-p38, p-ERK and p-JNK[74,75], implying that traditional Chinese herbal formulations could inhibit the progression of lung cancer by affecting the proliferation, invasion and migration and apoptosis of lung cancer cells. ShenlingBaizhu additive powder (SLBZ-AP) attenuated bone metastasis of lung cancer (BMLC)-induced pain and improved the survival of BMLC mice by inhibiting the proliferation and inducing apoptosis of SBC-5 cells through the PI3K-Akt-mTOR signalling pathway, as indicated by the downregulation of AKT, mTOR, P70S6 and VEGF expression[76]. Relevant studies have demonstrated that treatment with Naesohwangryeon-tang (NHT), Formula Yangyinjiedu (YYJD) and Ze-Qi-Tang (ZQT) could induce apoptosis of lung cancer A549 cells[77-79]. NHT could activate caspases and promote the generation of ROS to induce autophagy and apoptosis of A549 cells[77]. YYJD induced apoptosis of A549 cells by activating early growth response 1 (EGR1)[78]. ZQT arrests the cell cycle in the G0/G1 phase and induces apoptosis by down regulating p53 and p21 expression[79]. Wenxia Changfu formula (WCF) induced cell apoptosis, arrested the cell cycle in the G1 phase and reversed the drug resistance to DDP by downregulating the expression of integrin β1, FAK, PI3K and AKT[80]. This finding showed that integrin β1-PI3K-AKT pathway might contribute to the response of A549 cells to WCF. Yu Ping Feng San and Ginkgo Folium ($YPFS_{+GF}$) enhanced the anticancer effect of DDP in A549 cells. $YPFS_{+GF}$ effectively promoted the anticancer effect of DDP by modulating the Wilms tumor 1/major vault protein (WT1/MVP) axis and inhibiting the activity of the mTORC2/AKT pathway in A549 cells[81]. The treatment of H1650 cells with Jinfu'an (JFA) decoction downregulated the phosphorylation of S288 and elevated the level of Kaiso, which in turn inhibited the proliferation, migration and invasion of H1650 cells[82].

Bushen Shugan Formula (BSF), which has a potent therapeutic effect on the metastasis of lung cancer, inhibited proliferation, invasion and migration and induced G2/M arrested apoptosis in A549 cells by inhibiting EMT through the PI3K-AKT signalling pathway[83].

In recent years, many traditional Chinese herbal formulas for treating lung cancer have been reported. However, the limitation of Chinese medicine formulas cannot be ignored. Firstly, the effective ingredients of these formulas are not clear, which complicates the ability to elucidate the mechanisms of these medicines. Next, the efficacy of some Chinese herbal formulas remains unknown. Finally, the pharmacodynamics interactions between these formulas and other drugs are uncertain. Therefore, researchers need to do considerable works to solve these problems mentioned above.

CONCLUSION

Over the past few decades, a large number of studies have demonstrated that NPs exhibit significant anticancer capacity against lung cancer and inspire the development of anti-tumor drugs. NPs inhibit the proliferation, migration and invasion and induce the apoptosis of lung cancer cells by acting on various targets both *in vitro* and *in vivo*. However, few of these compounds have been used clinically due to their poor bioavailability. Therefore, further clinical trials are required to determine the clinical efficacy and management of these NPs for the prevention and therapy of lung cancer. Current review anticipated that NPs will have broad prospects in the treatment of lung cancer in the future.

SIGNIFICANCE STATEMENT

Lung cancer is ranked first of all cancer deaths for morbidity and mortality worldwide. Owing to the paucity of effective diagnostic and treatment strategies, it is necessary to find and develop new drugs or strategies for the treatment of lung cancer. Natural products (NPs) have excellent properties in the treatment of cancer, including lung cancer and are the most prolific source of inspiration for discovery of new drug leads. Therefore, the use of NPs may be a promising strategy for the treatment of lung cancer owing to the excellent properties and comparatively lower side effects. Current review discusses the mechanisms of NPs on lung cancer in order to providing a new insight for the cure and the development of new drugs for treating lung cancer.

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