# Natural Compounds as Versatile Potential Therapeutic Agents of Lung Cancer

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**Abstract**

Cancer is a condition in which cell proliferation becomes unregulated and leads to unchecked and non-terminating growth. It is considered one of the most important causes of death throughout the world. Among all sorts of cancers, lung cancer is the most common and foremost cause of mortality. Late diagnosis and lack of efficient therapeutic intervention are the chief players that cause limitations in the treatment of this type of cancer. Two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Various therapeutic approaches have been evaluated against lung cancer treatment such as radiotherapy, chemotherapy, surgery, and immunotherapy. Cancer cells manifest resistance against chemotherapeutic drugs and become unable to halt the metastasis of tumor cells. In this notion, natural compounds always act as an alternative approach with fewer side effects from history. Natural compounds such as phytochemicals have been shown as promising therapeutic agents due to their apoptotic, antioxidative, and anti-inflammatory activities. In this chapter, the role of these natural compounds is elaborated and well-defined with their therapeutic targets. Flavonoids, phenols, alkaloids, quinones, naphthaquinones, bibenzyl, and carotenoids have been extensively used that may target apoptotic signaling

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pathways, halt metastasis, prevent the formation of new blood vessels and invasion of a tumor to the surrounding area. Moreover, the synergistic effect of chemotherapeutic drugs and natural compounds also potentially inhibits the growth and progression of tumor cells. All these aspects have been discussed in the present segment.

**Keywords**

Natural compounds · Lung cancer · Apoptosis · Tumor · p53

## 10.1 Introduction

Cancer is a group of disorders that occur due to dysregulated cell proliferation and growth without terminating. Cancer is the second biggest cause of mortality worldwide. In specific organs, more than a hundred divergent types and subtypes of cancer have been found. Several types of cancers such as colorectal, lung, liver, breast, and gastric cancer have been reported in humans. There are commonly six physiological properties that characterized the development of tumors including evasion of apoptosis, growth signals self-sufficiency, growth-inhibitory signals insensitivity, sustained angiogenesis, unlimited replicative potential, and tissue metastasis and invasion [1].

### 10.1.1 Lung Cancer

Among all lung cancer is the most diagnosed and leading cause of cancer mortality throughout the world with a prevalence rate of 40% [2]. According to a recent estimate, 1.8 million people were diagnosed with lung carcinoma till 2012. The lack of reliable and appropriate therapeutic targets and biomarkers, late diagnosis, and incompetent drugs form a restriction in lung cancer treatment [3]. Lung cancer is further categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) which is three-fourths of all lung cancers. Smoking and older age are accounted for as the main causes of NSCLC [4].

The incidence of lung cancer correlates directly with the pattern of tobacco smoking (predominant risk factor). Greater than 80% of cases in men are reported due to exposure to tobacco, while in women the risk is less: in Northern Europe is about 70% and 45% throughout the world. Besides smoking, numerous other agents are known to increase lung cancer risk including exposure to chromium VI, chloromethyl ethers, nickel, asbestos, radon, or carcinogenic air pollutants, and environmental exposure to tobacco smoke [5]. Apoptosis acts as a defensive system that prevents an unregulated cell cycle. Bcl2 family genes such as Bad, Bax, Bik, and Bak are found to encourage cell death, whereas Bcl-XL halts apoptosis. Dimerization of Bcl-2/Bax is the principal step that regulates apoptosis through caspase

proteins and has a central role to play in induction, amplification, transduction, and execution of apoptotic stimuli within the cellular system [6].

### 10.1.2 Pathophysiology of Lung Cancer

Lung cancer originates via multiple processes including genetic and epigenetic modifications that drive the uncontrolled proliferation of cells and dysregulated apoptotic machinery. As tumor growth increases, it switches to expand the vascular network of blood vessels (angiogenesis) for oxygen and nutrient supply to the growing tumor. Following it, tumor cells start to invade the nearby surrounding tissues, and distant tissue sites to develop a new secondary tumor (metastasis). Additionally, driver mutations also play a key role in the growth and progression of tumor cells. For example, rearrangements of ROS1 (ROS proto-oncogene 1 receptor tyrosine kinase), ALK (anaplastic lymphoma kinase), and activating mutations in EGFR (epidermal growth factor receptor) contribute to NSCLC progression via activation of multiple signaling pathways including MEK/ERK, PI3K/Akt. These signaling pathways initiate a cascade of reactions and enhance proliferation, angiogenesis, and metastasis of tumor cells [7]. Similarly, VEGF (vascular endothelial growth factor) and MMPs (matrix metalloproteinases) also participate in angiogenesis and metastasis of lung cancer, respectively [8].

### 10.1.3 Conventional Treatments

Chemotherapy, radiation, immunotherapy, and surgery are mostly used treatment strategies to reduce the growth of lung cancer cells [9]. Radiation and surgery therapies are mostly used to cure early-stage lung cancer; however, these approaches are related to a high risk for cancer recurrence [10]. Chemotherapy is the common most treatment option for lung cancer. The choice of chemotherapeutic agents depends on the severity of tumor proliferation and progression. Platinum-based agents (carboplatin, cisplatin) act as the main component of chemotherapy (first line) despite the stage of lung cancer (Fig. 10.1). Cisplatin is a cytotoxic agent that induces DNA damage and activates the apoptotic pathway and most commonly used at the clinical level. However, cisplatin has been found to cause chemo-resistance and unfortunately unable to cure advanced lung cancer alone [11].

Other treatment agents (targeted therapy) include tubulin inhibitors (paclitaxel, docetaxel), topoisomerase I inhibitors (topotecan, irinotecan), and antimetabolites (pemetrexed, gemcitabine). Additionally, tyrosine kinase inhibitors including anti-VEGF antibodies (bevacizumab), and EGFR inhibitors (gefitinib, erlotinib) have been also used [12]. Unfortunately, the development of resistance in response to chemotherapy is the main obstacle in the treatment of lung cancer. Therefore, most emerging and effective therapy is the use of natural products that has the potential to be used as chemotherapeutic and chemopreventive agents with low or no side effects [13].

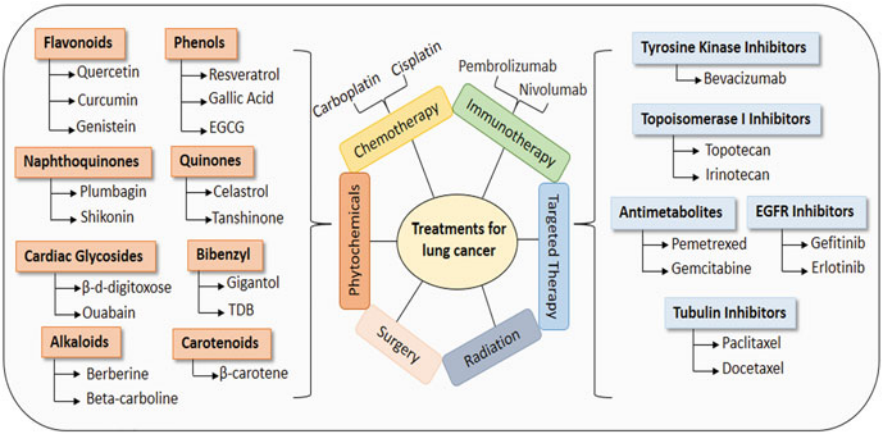



**Fig. 10.1** Treatment strategies for lung cancer

### 10.1.4 Natural Compounds

From the drug discovery history, natural products and their derived compounds are the alternative therapeutic approaches due to their ability to induce apoptosis in malignant cells as compared to normal healthy cells [14]. The main mechanism to control cancer is the induction of apoptosis to halt the proliferation of tumor cells. There are two main pathways targeted to cancer cells which are extrinsic and intrinsic apoptotic pathways [15]. Among natural products, phytochemicals are well known and promising therapeutic agents due to their anti-inflammatory and antioxidative activities. Apples, bananas, tomatoes, fish, herbal tea, white wine, and marine food are sources of phytochemicals that allow lung function recovery [16]. Phytochemicals include alkaloids (berberine, beta-carboline), phenols (resveratrol, EGCG, gallic acid), flavonoids (quercetin, curcumin, genistein), carotenoids (β-carotene), naphthoquinones (shikonin, plumbagin), quinones (celastrol, tanshinone), cardiac glycosides (Ouabain, β-D-digitoxose), and bibenzyl (gigantol, TDB) have been elaborated due to their extensive use in the treatment of lung cancer [17].

Moreover, various active anti-cancer constituents that are derived from vegetables including micronutrients (such as folic acid, vitamin E and C, selenium), and bioactive compounds such as glucosinolates, isothiocyanates, and indoles have been found to contribute in reducing the risk of cancer. These agents either exert direct action through radical scavenging or indirect action via interacting with the body's molecular and metabolic processes to prevent cancer metastasis [5].

This chapter focuses on the molecular targets of natural compounds targeting apoptosis, metastasis, angiogenesis to prevent the progression of lung cancer. In this regard, beneficial constituents of natural compounds with anti-lung cancer activities and their chemotherapeutic potential have been discussed in detail.

## 10.2 Molecular Targets of Natural Compounds

The unique mechanism of natural compounds provides the knowledge of their useful activity against cancer cells. The molecular mechanism of natural compounds with anticancer properties plays an important part in the development of drug-associated therapeutic approaches for cancer treatment. Target molecules for lung cancer treatment are given below in detail.

### 10.2.1 Natural Compounds Targeting Apoptotic Pathways

Apoptosis, a series of events involves morphological alterations such as blebbing of plasma and nuclear membrane, shrinkage of the cell, nuclear lamina dissolution, and various biochemical processes responsible for critical activation of apoptosis. Medicinal plants from potent active compounds act as good inducer of apoptosis in lung cancer cells [18]. Different herbs (Thai) such as *Croton oblongifolius*, *Erythrophleum succirubrum,* and *Bridelia ovata* were found to induce cytotoxicity in A549 lung cancer cells [19]. Further, *Citrus aurantium* (a mixture of flavonoids) was reported to mediate p-p53 and cleaved caspase-3 to induce apoptosis in NSCLC (A549) cells [20].

### 10.2.2 Natural Compounds Arrest Angiogenesis

Angiogenesis is a process of the formation of new blood vessels from pre-existing vessels. It takes the most important part of the growth and spread of lung cancer because it significantly induces the growth and development of novel blood vessels [21]. Hence, blockade of angiogenesis is found as a potent therapeutic target for lung cancer cells. Vascular endothelial growth factors (VEGF) associated with vascular endothelial development contribute a key role in angiogenesis. Along with VEGF, other related indirect angiogenic factors, including platelet-derived growth factor (PDGF), tumor growth factor-alpha (TGF-α), and basic fibroblast growth factor (bFGF) also participate in the spread of a tumor. Various clinical trials have presented VEGF-targeted therapies to prevent the spread of cancer cells via inhibiting angiogenesis [18, 22].

### 10.2.3 Natural Compounds Attenuating Metastasis

Metastasis is the most important characteristic of malignant neoplasm and the leading cause of mortality in cancer patients. Tumor cell intravasation, dissociation, invasion, spread to distant organs, and increased motility to arrest cells of the small vessels are all related to tumor metastasis. MMPs (Matrix metalloproteinases) are extracellular matrix proteolytic enzymes and related to invasion and metastasis of

cancer. Among all members of the MMP family, MMP-9 and MMP-2 significantly alter the metastatic processes [23, 24].

Several natural product molecules have been reported to target the metastasis of tumor cells to prevent the spread of cancer. Epicatechin-3-gallate derived from green tea was revealed to upregulate E-cadherin and oppose the TGF-β1-induced EMT. Moreover, baicalein and wogonin (flavone component) in *Scutellaria baicalensis* were reported to induce downregulation of MMP-9 and the MMP-2 in both the A549 and H1299 cells [25].

### 10.2.4 Natural Compounds Targeting ROS

Reactive oxygen species (ROS) signaling is recently considered the main research focuses on lung cancer cells [26]. Few studies mentioned the use of herbal extracts can reduce active oxygen species in lung cancer cells. Histone deacetylase (HDAC) was reported to regulate oxidative stress pathways and can be used with curcumin (*C. longa* L.), and epigallocatechin 3-gallate (*Camellia sinensis*), and sulforaphane (*Brassica oleracea*) to combat NSCLC [18].

## 10.3 Anti-Lung Cancer Natural Compounds

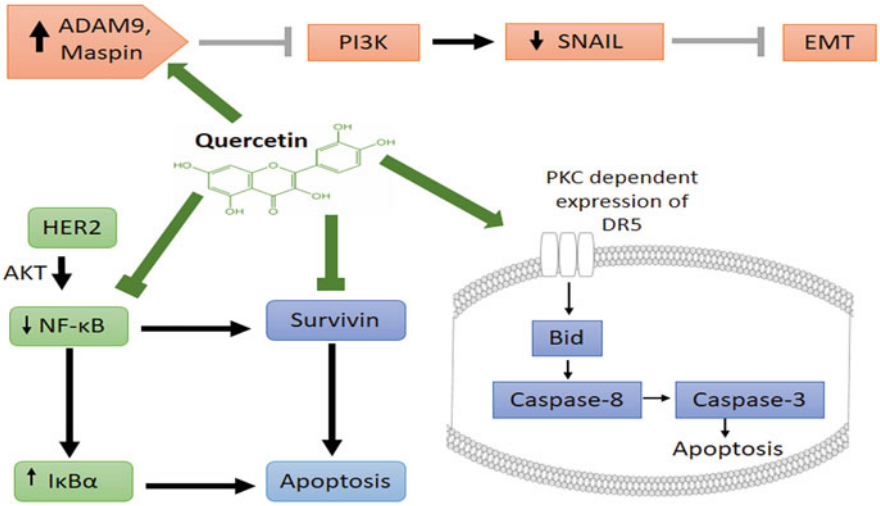
Natural compounds-derived phytochemicals are considered as an alternative approach for therapeutic development against lung cancer. Phytochemicals undeniably have the potential to improve the outcome of lung cancer treatment with fewer side impacts. A brief overview of natural products with non-apoptotic or apoptotic effects is described below.

### 10.3.1 Flavonoids and Lung Cancer

Flavonoids are polyphenolic compounds associated to reduce the risk factor of different types of lung cancer such as lung cancer and found in vegetables and fruits. Flavonoids have many beneficial effects and altered molecular mechanisms in tumor cells as well as inhibit the production of reactive oxygen species. Of these, some of the important flavonoids are discussed below [27].

#### 10.3.1.1 Quercetin

Quercetin (3,3,4′,5,7-pentahydroxyflavone) is a potent antioxidant and black tea, green tea, vegetables, fruits, and medicinal plants including *Euonymus alatus* (Thunb.) Sieb are a rich source of quercetin. Among all of the above mentioned sources, the apples and onions are excellent derivatives of quercetin. Various studies have reported the beneficial role of quercetin as an anti-inflammatory, anti-hypertensive therapeutic, and preventive agent for cancer cells. Quercetin involved in the cell cycle inhibition and death receptor signaling pathway in H460 cells in NSCLC, as



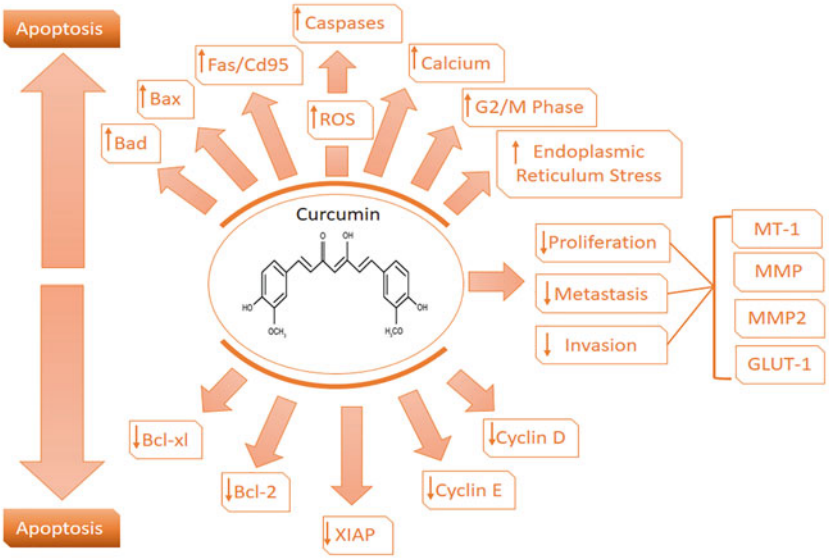

PI3K: Phosphoinositide 3-kinase; PKC: Protein kinase C; AKT: Protein kinase B; SNAIL: Zinc finger transcription factor; NFκB: Nuclear factor kappa B; IκBα: I- kappa B alpha; ADAM-9: Disintegrin and metalloproteinase domain-containing protein 9; Bid: Pro-apoptotic protein; Caspase-3: Protein; Caspase-8: Protein; HER2: human epidermal growth factor receptor-2; DR5: Death receptor-5; EMT: epithelial to mesenchymal transition

**Fig. 10.2** Anti-lung cancer mechanistic approach of quercetin

revealed in a recent study. In fact, quercetin sensitizes apoptosis (TRAIL-induced) in NSCLC cells through two main independent pathways including suppression of survivin (Akt-mediated) expression and induction of death receptor-5 (DR5) through PKC (Fig. 10.2). Moreover, quercetin was found to downregulate NF-κB expression and upregulate IκBα (inhibitor of NF-κB) at both protein and mRNA levels and potentiate apoptosis in H460 cancer cells [28, 29]. Cytochrome P450 enzymes including CYP1A1 and CYP3A4 play a crucial role in the bioactivation of polycyclic aromatic hydrocarbons carcinogens in squamous cell lung carcinoma. Since quercetin can modify the CYP1A1 genotype via inhibiting P450 enzymes and it is strongly suggested by clinical studies [30]. Moreover, quercetin has also been found to upregulate Snail independent ADAM9 expressions and maspin to inhibit Snail dependent-Akt activation to suppress EMT in human NSCLC cells [31].

#### 10.3.1.2 Curcumin

Curcumin is a bioactive component of the natural dietary compound turmeric spice and has the potential to exert anticancer effects on several types of cancers including lung cancer [32]. As suggested by in vitro studies via p53 independent and mitochondria-dependent pathways, curcumin induces apoptosis (Fig. 10.3). In the G2/M phase, curcumin strongly upregulates cell cycle arrest, Bad, Bax, FAS/CD95 and downregulates cyclin E, D (cell cycle regulator), Bcl-xL, Bcl-2, XIAP protein




G2/M Phase: Cell cycle phases; Bad: BCL2 associated agonist of cell death; Bax: BCL2 associated X protein; FAS/CD95: Tumor necrosis factor receptor; Cyclin D/E: Cell cycle regulator protein; Bcl-xL: Anti-apoptotic protein; Caspases: Apoptotic protein; Bcl-2: B-cell lymphoma 2; XIAP: X-Linked Inhibitor Of Apoptosis; MT-1: Metallothionein-1 protein; MMP: Matrix metalloproteinases; MMP2: Matrix metalloproteinases-2; GLUT-1: Glucose transporter-1; Ca: Calcium; ROS: Reactive oxygen species

**Fig. 10.3** Anti-lung cancer mechanistic approach of curcumin

expression and also able to increase intracellular calcium, endoplasmic reticulum stress, ROS which ultimately leads to interrupt potential of mitochondrial membrane and induces activation of caspases in the cultured H460 cells [33–36]. Besides potent apoptotic effects of curcumin, it also induces an inhibitory effect on tumor survival as well as progression [37]. Additionally, in lung A549 cells curcumin was found to suppress proliferation, metastasis, and invasion via reducing MT-1, MMP, MMP2, and GLUT-1 for cancer intervention [38].

#### 10.3.1.3 Genistein

Genistein (GEN), an isoflavone present in soybeans, soy sauce, soy milk, and tofu, enhances autophagy and apoptosis of cancer cells especially in lung cancer, breast cancer, lymphoma, and gastric cancer [39, 40]. It also enhances the efficacy of radiotherapy in tumor cells and also attenuating inflammatory injuries in normal cells that are caused by ionizing radiation. Autophagy involves the lysosomal degradation pathway which mediates the death of cancerous cells. Similarly, GEN inhibits Bcl-xL translocation and is found to promote apoptosis in NSCLC cells via dissociating Bcl-xL from Beclin-1 as revealed from in vitro and in vivo study [41].

#### 10.3.1.4 Silymarin

Silymarin is obtained commonly from *Silybum marianum* L. Gaertn. (milk thistle) plant and has anticancer properties. Silymarin has no side effects on non-malignant cells but toxic against malignant cells [42]. It is also found that silymarin can restore or reactivate E-cadherin expression in H460 and A549 cells. In fact, E-cadherin expression is directly linked to reducing NSCLC cell migration. Thus, silymarin treatment significantly contributes to regulating HAT activation and HDAC inactivation to control the expression of E-cadherin. Additionally, silymarin also targets transcription factor ZEB1 that downregulates HDAC1/2. Anti-lung cancer activity of silymarin has been explored in NSCLC cell lines (H460 and A549) that potentially correlate to the level of miR-203 (tumor suppressor) expression. Conclusively, silymarin treatment significantly regulates proliferation, invasion as well as metastasis of tumor cells via targeting particular genes [43, 44].

### 10.3.2 Alkaloids and Lung Cancer

#### 10.3.2.1 Sophoridine

Sophoridine (SRI) being quinolizidine alkaloid possesses a wide range of beneficial properties such as anticancer, anti-inflammatory, antiviral, and also mediates cardiac protection. Extract of *Sophora alopecuroides* L. is a source of sophoridine. Food and Drug Administration (FDA) of China has approved sophoridine injections as a treatment strategy for malignant trophoblastic tumors in 2005. Recently, SRI was also reported to exert an inhibitory effect on malignant tumors. Growing evidence demonstrated that the anticancer activity of SRI is due to its ability to activate p53 signaling in gliomas. Along with p53, the hippo pathway dysregulation also contributes to lung cancer tumorigenesis via regulating the YAP–TEAD complex. MDM2 acts as a down-regulator of p53 and mediates p53 degradation via ubiquitination. SRI inhibited MDM2-mediated p53 ubiquitination that is the potential target site to prevent turnover of the p53 signaling pathway. Of note, a recent study found that SRI promotes apoptosis and suppresses migration and invasion of NCI-H1299 cells independent of p53 and Hippo signaling pathways [45, 46].

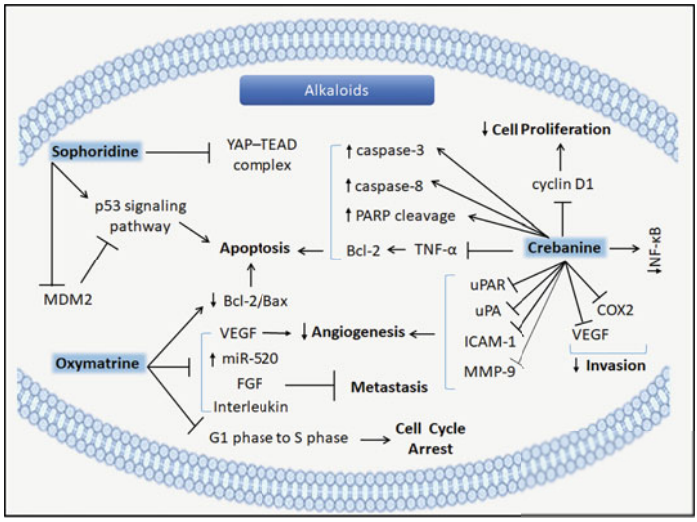
#### 10.3.2.2 Crebanine

Crebanine is one of the aporphine alkaloids isolated from *Stephania venosa* and has many pharmacological activities such as antimicrobial, anticancer, and antiarrhythmic. It presents anticancer properties via suppressing NF-κB activation and sensitizing TNF-α induced cell death of cancer. Of note, NF-κB is a regulator of tumor progression and development as well as a mediator of inflammation and activated by TNF-α which acts as a switch in creating a link between cancer and inflammation. In addition, crebanine also enhances TNF-α mediated apoptosis via activation of caspase-3, caspase-8, and PARP cleavage. It was also revealed that crebanine inhibits TNF-α induced Bcl-2 (anti-apoptotic), cyclin D1 (cell proliferation), MMP-9, uPA, uPAR, and ICAM-1 (invasion) and COX2, VEGF (angiogenesis) gene expression, thus reduces NF-κB activation in human lung adenocarcinoma

cells A549. Hence, crebanine acts as a strong agent in the treatment of lung cancer [47, 48].

#### 10.3.2.3 Oxymatrine

Oxymatrine (OMT) is isolated from "*Sophora flavescens*" and acts as a potent constituent of traditional Chinese medicine. It has multiple beneficial properties including anti-inflammation, anti-tumor, antifibrosis, and antivirus [49, 50]. Numerous in vitro studies have proven that OMT can induce cell cycle arrest, inhibit not only tumor cell proliferation but also differentiation, invasion, metastasis, and promote apoptosis [51]. Experiments showed that OMT blocks A549 lung adenocarcinoma cell line proliferation in vitro and also causes cell cycle arrest via preventing entry from the G1 phase to the S phase and keeps them in the G0 phase. It was found that OMT could decrease the Bcl-2/Bax ratio in the A549 lung cancer cell line (Fig. 10.4). Bioinformatic analysis revealed that OMT has a novel use due to its impact on the regulation of miRNA expression. It may inhibit the major signaling pathways including VEGF, interleukin, cadherin, apoptosis, and FGF to regulate metastasis as well as angiogenic properties of lung tumors. It was also confirmed that OMT treatment upregulates miR-520 significantly, thus strongly associated with the prevention of metastasis and the growth of lung cancer [52].




Bcl-2/Bax: BCL2 associated X protein; Cyclin D 1: Cell cycle regulator protein; uPA: Urokinase; MMP-9: Matrix metalloproteinases-9; PARP: Poly (ADP-ribose) polymerase; COX-2: Cyclooxygenase-2; MDM2: E3 ubiquitin-protein ligase; ICAM-1: Intercellular Adhesion Molecule 1; Caspase-3: Protein; Caspase-8: Protein; NFκB: Nuclear factor kappa B; TNF-α: Tumor necrosis factor-alpha; FAS/CD95: Tumor necrosis factor receptor; Upar: urokinase-type plasminogen activator receptor ; VEGF: Vascular endothelial gowth factor; FGF: Fibroblast growth factor; YAP-TEAD: Yes-associated protein- TEAD transcription factor complex; Interleukin: Protein; p53:Tumor protein; miR-520: tumor-related miRNA

**Fig. 10.4** Alkaloids and lung cancer

#### 10.3.2.4 Berberine

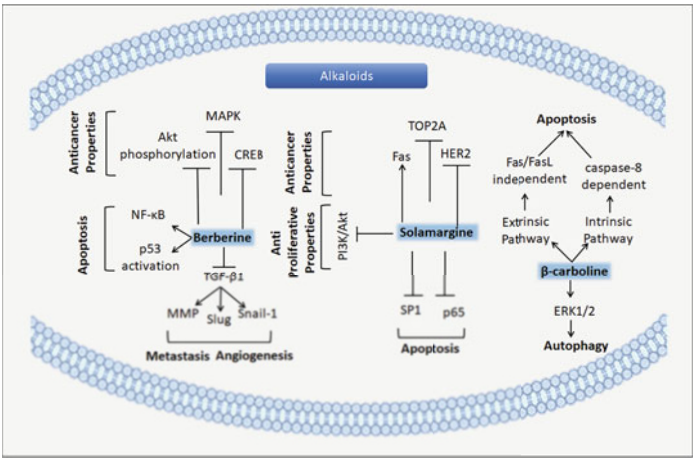
Berberine (2, 3-methylenedioxy-9, 10-dimenthoxyproto-berberine chloride) is isoquinoline alkaloid and derived from berberis species including *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), *Tinospora cordifolia*, and *Berberis aristata* (tree turmeric). Berberine (BBR) is widely used as an anti-inflammatory, antifungal, and antibacterial agent [53, 54]. BBR also possess anti-lung cancer activity via inhibition of cell migration, proliferation, apoptosis, and invasion through multiple pathways [55]. BBR is found to treat A549 cell line in a dose and time-dependent manner, as explored by in vitro and in vivo study. Besides, it has also shown that BBR suppresses TGF-β1-induced EMT expression of Slug, Snail-1, and MMP (matrix metalloproteinases), thus inhibits tumor metastasis and angiogenesis. BBR has potential effects on NFκB signal activation, reactive oxygen species generation, RNA or DNA binding, p53 activation, mitochondrial function, MMPs regulation, and inhibition of DNA topoisomerase activity [56]. BBR was also isolated from Rutaceae family plants and exhibited anti-lung cancer properties to treat A549 cancer cells via inhibiting Akt phosphorylation, MAPK, and CREB in a mouse model [57].

#### 10.3.2.5 Solamargine

Solamargine (SM) is a glycoalkaloid and typically extracted from the traditional herb of *Solanum lycocarpum*. It possesses anti-inflammatory, antiproliferative, and antiviral activity and is used against numerous types of cancers including lung cancer. SM downregulates TOP2A (topoisomerase II alpha), HER2 (human epidermal growth factor receptor-2) and upregulates Fas expression to accelerate apoptotic cell death in NSCLC A549 cells [58]. It is found that SM inactivates PI3K/Akt signaling, therefore regulates gene expression and inhibits proliferation and growth of cancer cells. Additionally, SM possesses anti-lung cancer activity by reducing the SP1 transcription factor and p65 level [59, 60].

#### 10.3.2.6 Beta Carboline

Beta-carbolines (β-carboline) are found in various medicinal plants including *Banisteriopsis caapi*, *Peganum harmala*, *Passiflora incarnata*, and *Passiflora edulis*. β-carboline alkaloids have anti-tumor activity and cytotoxic effects on various cancer cells [61]. Harmol is a β-carboline that causes apoptosis in NSCLC H596 cells via the extrinsic pathway (Fas/FasL independent), and the intrinsic pathway (caspase-8 dependent) in humans. In H596 cells, harmol rapidly induces apoptosis within 3 h of treatment [62]. However, recent studies have revealed that harmol kills A549 lung cancerous cells via autophagy instead of apoptosis. Numerous studies reported that the ERK1/2 pathway significantly mediates autophagy (Fig. 10.5). Indeed, harmol also induces autophagy through the ERK1/2 pathway in A549 cells thereby, suggested the key role of harmol in the treatment of lung cancer cells [63, 64].




PI3K:Phosphoinositide 3-kinase; AKT: Protein kinase B; ERK: Extracellular signal-regulated kinase ; MAPK: mitogen-activated protein kinase; MMP: Matrix metalloproteinases: TOP2A: Topoisomerase 2A; Snail-1: Zinc finger transcription factor; Slug: transcription factor; NFκB: Nuclear factor kappa B; TNF-β: Tumor necrosis factor- β ; Caspase-8: Protein; p53:Tumor protein; p65: Protein ; SP1: Specificity proteins; Fas: Protein; CREB: cAMP response element-binding protein; HER2: human epidermal growth factor receptor-2

**Fig. 10.5**

### 10.3.3 Polyphenols and Lung Cancer

Polyphenols are commonly present in vegetables, fruits, tea, wine, and whole grains. Till yet, 10,000 polyphenolic natural compounds have been recognized [65]. They are further classified into four groups, including flavonoids, stilbenes, phenolic acids, and lignans [66]. Polyphenols have a high binding affinity with oncogenic molecules and possess anticancer activities. The imperative anti-tumor mechanism of polyphenols in lung cancer vigorously depends on activation or inhibition of certain intrinsic signaling agents such as p53, p21, Bax (pro-apoptotic effectors), miR-622, miR-192-5p (tumor suppressor) and PI3K, MEK, ERK, NFκB (signaling pathways), Bcl2, Bcl-xL (anti-apoptotic effectors), respectively [52].

#### 10.3.3.1 Resveratrol

Resveratrol is a stilbenes phytoalexin and first time isolated from *Veratrum grandiflorum* (White hellebore). Resveratrol (3,5,4′-trihydroxy-trans-stilbene) presented health conferring effects such as anti-inflammatory, antioxidant, anticarcinogenic as well as antidegenerative activities [67, 68]. It inhibits cellular proliferation, induces cell cycle arrest and apoptosis, and also inhibits invasion and metastasis of lung cancer. Moreover, it also exerts inhibitory growth effects on lung cancerous cells through the upregulation of Smad 7 and downregulation of Smad 2/4 that are major components of transforming the growth factor-beta/Smad signaling

pathway. It causes cell cycle arrest in the G1 phase via mediating activation of caspases, suppresses mitochondrial permeability, and increasing p53, p21, and p27 (cyclin-dependent kinase inhibitor) expression at both protein and gene level [69]. In H460 and 16HBE-T bronchial epithelial cells of humans, a previous study found that resveratrol regulated miRNA expression to mediate apoptosis and cell proliferation of tumor cells. Additionally, resveratrol was examined to mediate its anti-tumor effect via regulating miR-520 h in A549 and CL1-4 lung carcinoma cells [70]. Considering the anti-tumor effects; resveratrol, a similar synthetic product BCS (3,4,5-trimethoxy 4 V bromo-cis-stilbene) has been introduced that possesses a more potent effect (1100 times) than resveratrol to cause inhibition of A549 cells [71].

#### 10.3.3.2 Ellagic Acid

Ellagic acid, a phenolic constituent is found in strawberries, raspberries, green tea, pomegranates, grapes, nuts, and has similar potency against lung cancer cells like resveratrol. Among grapes, red wine is the greatest source of higher concentration of ellagic acid [72–74]. Ellagic acid (EA) exhibits both antioxidative and anti-tumor activities [75]. EA indicates in vitro and in vivo anti-tumor activities through inhibiting the proliferative nature of tumor cells via cell cycle arrest. Moreover, EA also induces apoptosis, inhibits angiogenesis, and ameliorates inflammation [76]. Recent research explored that EA has also the ability to control oncoprotein CIP2A (cancerous inhibitor of protein phosphatase 2A) level and induced autophagy in lung cancerous cells. Moreover, EA suppresses p-mTOR, p-Akt, p-P70S6K, Notch, and Shh pathways to mediate cell growth of tumor cells in vivo and in vitro [77].

#### 10.3.3.3 Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) is a principal component of green tea (*Camellia sinensis*), reveals anti-inflammatory, antiproliferative, antioxidative, and antimutagenic activities [78]. EGCG can inhibit the growth rate of tumor cells, as demonstrated in various types of cancers [79]. EGCG has been found to suppress the growth of cancer cells in various NSCLC cell lines [80]. EGCG follows the AMP-activated protein kinase activation pathway to inhibit proliferation, migration, colony formation, and invasion of lung cancer cells (H1299) in human in vivo [81]. Additionally, EGCG also suppresses the growth of lung cancer cells through the upregulation of miR-210 expression [82].

### 10.3.4 Bibenzyl and Lung Cancer

#### 10.3.4.1 4, 5, 4′-Trihydroxy-3, 3′-Dimethoxybibenzyl (TDB)

*Dendrobium ellipsophyllum* is a source of 4,5,4′-trihydroxy-3,3′-d imethoxybibenzyl (TDB), that is used for sensitization of lung cancer cells via inhibiting epithelial to mesenchymal transition (EMT) and prevent cancer cell metastasis, invasion, and migration [83]. Snail, vimentin are biomarkers of EMT that are suppressed by TDB non-lethal concentration. This suppression of EMT

leads to induce anoikis as well as causes a reduction in cell growth rate via reducing p-AKT and p-ERK signaling [25, 84]. Moreover, TDB is found to mediate apoptosis in human lung carcinoma through activation of caspase-3 and phosphatidyl-serine localization on the outer surface of the cell membrane. TDB has been reported to restore p53 signaling via activating Bax, Bcl-2 associated X protein, reducing Bcl-2, Mcl-1 in human lung cancer cells including H460, H23, and H292 [83].

#### 10.3.4.2 Gigantol

Gigantol is isolated from the *Dendrobium draconis*, *Thai orchid*, and possesses several pharmacological properties including anti-inflammatory, antiplatelet aggregation, and induces cancer cell death [85–87]. Recent research has clearly mentioned that gigantol follows Cav-1 dependent pathway to suppress cell migration in lung cancer. Cav-1 (caveolin-1), and Cdc42 (cell division cycle 42) are well-known signaling proteins that play a vital role in cell migration. Many cancer types such as lung cancer represent a high level of Cav-1, and it has been seen in human lung carcinoma that overexpression of Cav-1 increases the motility of H460 cancer cells [88, 89]. Interestingly, gigantol is found to be capable of downregulating Cav-1 expression which can lead to the attenuation of Cdc2 expression and Akt phosphorylation and, thereby, suppress filopodia formation. Hence, the results of the study revealed that gigantol has anti-migratory activity in lung cancer cells and can overcome cancer metastasis [90].

### 10.3.5 Carotenoids and Lung Cancer

#### 10.3.5.1 Crocin

Crocin is abundantly present in saffron (*Crocus sativus*) stigma and possesses anti-tumor activity through mediating growth inhibition of tumor cells. Crocin is water-soluble and presents minor or no side effects, thereby act as a suitable chemotherapeutic agent. Recently, it is revealed that Crocin is the main active carotenoid in saffron that is responsible for anti-lung cancer properties and has shown cytotoxic and antiproliferative effects in A549 cells as compared to L929 (non-malignant) cells [61].

#### 10.3.5.2 Astaxanthin

Astaxanthin is found in abundant amounts in seafood shrimp, salmon, red yeast, and microalgae, possesses several biological activities such as anti-inflammatory, anticancer, antioxidant, and also shows health benefits effects in neurodegenerative, gastrointestinal, and liver diseases [91]. Astaxanthin reduces the Bcl-2 level and enhances the Bax level, as revealed by a recent study. It was also seen that astaxanthin inhibits JAK-1 and STAT-3 phosphorylation that are involved in regulating the cell growth in NSCLC-A549 cells, thus suppresses the growth rate and induces apoptosis [92]. Additionally, astaxanthin has been found to downregulate TS (thymidylate synthase) expression in NSCLC cell lines including H1650 and H1703 via reducing MKK1/2-ERK1/2 activity [93]. Astaxanthin

treatment is found to decrease the p-AKT level, thereby revealed to inhibit cell proliferation and viability of NSCLC cells (A549, H1703) in a dose-dependent manner [94].

## 10.3.6 Naphthoquinones and Lung Cancer

### 10.3.6.1 Shikonin

Shikonin (SHK), an active naphthoquinone and main ingredient of purple gromwell (*Lithospermum erythrorhizon*) is a well-known natural product for its pharmacological and biological activity [95]. It has antimicrobial, anti-inflammatory, antiplatelet, antiangiogenic, anti-tumor, and anti-infection actions. SHK has been revealed by clinical studies as well as in vivo and in vitro studies as an anti-lung cancer agent [96, 97]. It exerts cytotoxic effects through the increasing generation of reactive oxygen species that trigger caspase-dependent apoptotic pathways and also downregulates NFκB to mediate MMP levels which ultimately reduce tumor invasion, and survival [98]. SHK has anti-invasive and anti-migratory potential, as significantly suggested by a recent study in lung cancer cells (HCC827). The results of this study mentioned that SHK causes EMT suppression and inhibition of c-Met expression through inhibition of PI3K/Akt and ERK signaling pathway [99]. However, SHK has been explored as a potent cytotoxic agent against lung cancer A549 cells via initiating necrotic and apoptotic pathways [97].

### 10.3.6.2 Plumbagin

Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) is derived naturally from *Plumbago zeylanica* (root) with numerous medicinal properties including anticancer, anti-migratory, and cytotoxic activity. Plumbagin (PLB) has shown antiproliferative activity in A549 cells via arresting tumor cells in S, G2, and M phase and induces apoptosis as well as enhances ROS production via mediating mitochondrial downstream molecules such as caspase-9 and caspase-3 [100, 101]. In addition, a study revealed that PLB treatment inactivates PI3K/Akt signaling, downregulates Bcl2, and upregulates Bax in H23 and A549 lung cancer cells, thus induces autophagic cell death [100]. Another study also explored that PLB suppresses human LCLC (Large cell lung cancer) cell lines including L9981 and NL9980 by inhibiting IL-6/STAT3 signaling [102].

## 10.3.7 Indole 3-Carbinol and Lung Cancer

Indole 3-carbinol (I3C) belongs to glucobrassicin derivative and found in cruciferous vegetables including cauliflower, brussels sprouts, broccoli, and cabbage. It acts as an anti-tumor agent against various cancers such as liver, gastric, and lung by suppressing tumor cells proliferation, invasion, angiogenesis. Additionally, I3C also modulates carcinogen metabolism and induces apoptosis to prevent the growth of cancer cells. 3,3-diindolylmethane is the main active ingredient of I3C that is

produced when I3C undergoes condensation reactions in the stomach [103]. Various studies highly mentioned the key role of I3C treatment in lung carcinoma [104]. I3C suppresses the level of Cox-2, phospho-NF-κB, FAS, and phospho-Akt but increases proteolytic cleavage of PARP, caspase-3/8, cyclin-D1, p-53, and p21 in lung cancer cells [105, 106]. Further, I3C is also revealed to downregulate overexpression of different microRNAs particularly miR-21 (tumor promoter) as a chemopreventive strategy in lung tumors [107]. ERK, Akt, and NF-κB pathways have been explored to play a key role in the maintenance of cell proliferation, survival, and expression of inflammation-associated genes, respectively. All of these pathways are found to be activated in normal alveolar and bronchial cells and even in NSCLCs. I3C plays a critical role in regulating NFκB, Akt, and ERK pathways, as suggested by not only the A/J mouse model but also by human bronchial epithelial cells (HBECs) and alveolar basal epithelial cells A549 [107, 108].

## 10.4 Natural Compounds as Chemotherapeutic Drug Sensitizer

Although various natural compounds have been well recognized and well researched about their health-related beneficial effects, it was also strongly suggested that combinatorial treatment of chemotherapeutic drugs and naturally occurring active ingredients can serve as the best therapeutic intervention to eradicate metastasis and apoptosis of lung cancer cells. The synergistic effect of phytochemicals and drugs have been described below.

### 10.4.1 Genistein-Trichostatin A Combined Effect

Genistein found in soybeans and soybeans related products may possess a protective role against lung cancer and numerous other cancers. Genistein has an enhancing effect on trichostatin A-induced apoptosis, suggesting a strong combination to control cell cycle arrest in A549 cells. Several studies demonstrated that genistein enhances apoptosis via p53 upregulation in NSCLC cells [109]. TSA is a potent HDAC inhibitor, thus contributes to inhibiting tumorigenesis via reducing the HDACs level. Genistein alone at 20 and 50μM concentration has an ability to upregulate histone acetylation (HAT) and p300 expression in A549 cells. However, TSA and genistein synergistic effect upregulate p53 along with HAT in H460 cells in a dose-dependent manner more efficiently than genistein alone [110].

### 10.4.2 Baicalin-Cisplatin Combined Effect

Cis-diamminedichloroplatinum (cisplatin, DDP) is the first member of anticancer drugs and is used as an intermediate and standard therapy for lung cancer. Cisplatin forms identical cross-links between DNA guanine bases and is used to treat several

other types of cancers including lung carcinoma via triggering apoptotic pathways [111]. However, toxicity and resistance are major side effects of DDP and are widely reported against lung cancer therapy [112]. Natural compound Baicalin belongs to a class of phytochemical flavone glycoside and abundantly found in *Scutellaria lateriflora* and *Scutellaria baicalensis* [113]. Baicalin has been shown as an anxiolytic agent, apoptosis enhancer, inhibitor of prolyl endopeptidase, and malignant tumor proliferation [114]. Downregulation of Microtubule affinity-regulating kinase 2 (MARK2) and p-Akt are the target sites of Baicalin to reduce DDP induced resistance against lung cancer therapy. Indeed, MARK2 directly interacts with Akt that is the main component of PI3K/Akt/mTOR signaling which plays a significant role in the progression and proliferation of cancer. So, Baicalin induced inhibition of MARK2 and Akt suppresses the activation of this signaling pathway and ultimately leads to enhancing the potent effects of DDP to prevent metastasis and invasion of lung cancer cells [115, 116]. Further, in NSCLC, IL-6 signaling also enhances DDP resistance via upregulating Akt expression [117]. Moreover, it has been revealed that the synergistic relation of DDP and baicalin at a dosage of 4 and 8μg/ml after 48 h incubation has an inhibitory effect on tumor cell invasion of A549 lung cancer cell line as compared to alone baicalin or DDP treatment. All these findings strongly suggest that baicalin adjunct of DDP and a candidate for lung cancer therapy [116].

### 10.4.3 Sophoridine-Cisplatin Combined Effect

Cisplatin is platinum-based chemotherapy and used against advanced lung cancer treatment. Along with beneficial effects, such type therapy has also presented toxic effects and has become a critical challenge for the scientist to develop natural based therapy with no or minimal hazardous effects as discussed in Sect. 4.2. It has also been reported that 85% of patients face neutropenia [118] and 50% were unable to accomplish treatment with cisplatin therapy alone [119]. Based on this, it was evaluated in a recent study that Sophoridine (SRI) and Cisplatin fusion can improve NSCLC cell treatment and diminish the side effects of chemotherapy [46].

### 10.4.4 Noscapine-Cisplatin Combined Effect

Noscapinoids (Nos) are antimicrotubule agents, suppress the proliferation of cells, and are used in the treatment of various cancers. Noscapine is derived from *Papaver somniferum* L. (opium flower) and used to arrest the G2/M phase in various types of cancers including breast cancer and lung adenocarcinoma (A549 cells) [120, 121]. Nos is found to attenuate microtubule dynamics to halt cell cycle via activating mitotic checkpoints. Further, Nos significantly reduce tumor volume in NSCLC in a dose-dependent manner. Nos-Cis has potential against tumor cells of the lung synergistically, as reported by previous researches. Co-treatment of Cis and Nos showed a significant increase in apoptosis, PAPR cleavage, and caspase 3 as compared to alone. Nos + Cis combination is found to cause cytotoxicity via both

intrinsic and extrinsic apoptotic pathways as well as activation of growth-inhibitory molecules against lung tumor cells [122].

## 10.5 Lung Cancer Stem Cells

In 1977 the concept of CSCs (cancer stem cells) was familiarized and has become a very concerning topic in cancer study nowadays. CSCs are a minor erratic fraction of the whole population of cancer cells that reveal high tumorigenic potential [123, 124]. Cancer stem cells were first known as "cancer-initiating cells" as they are assumed as the main cause of cancer. The features of CSCs, an essential role in pouring hostility of cancer contain their self-renewal ability, differentiation, migration features, great tumorigenicity, high assault, and conflict to the chemotherapy. According to these features, CSCs are assumed as chief arbitrator of all the malignance hallmarks comprising elevated metastasis potential, elevated tumorigenic, conflict to the chemotherapy, and cancer deterioration [125].

### 10.5.1 Key Features of Cancer Stem Cells

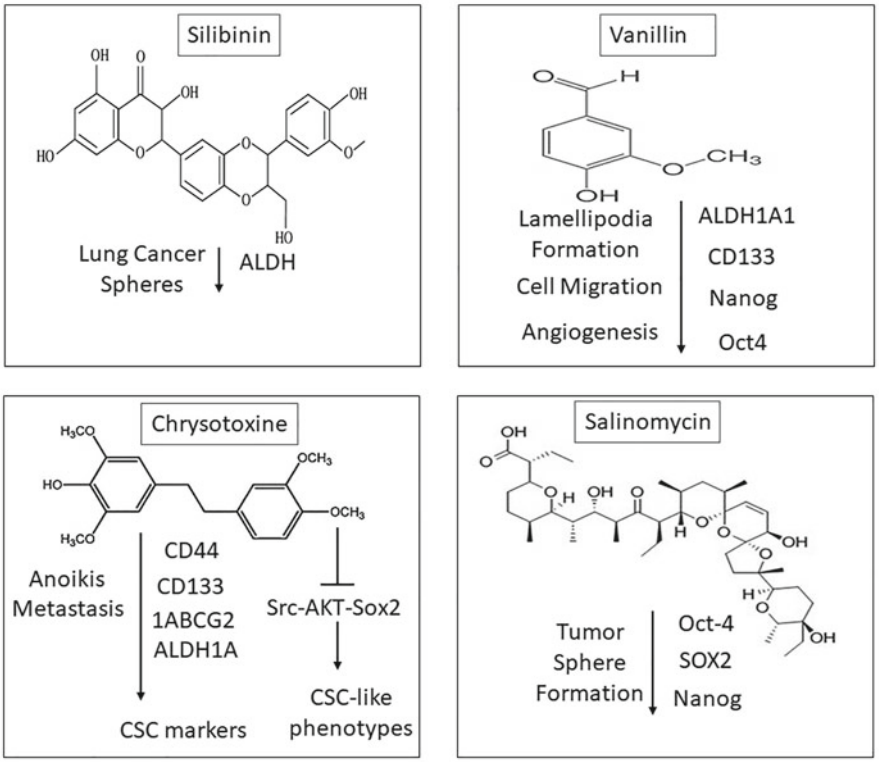
Cancer stem cells (CSCs) are assumed to possess characteristic features such as self-renewal capacity, heterogeneity, and high tumorigenic potential which make it distinguished from normal cells. Detail of each feature is given below:

1. Self-renewal capacity: CSCs have a distinctive ability of self-renewal (like normal stem cells). They divide rapidly and give rise to identical daughter cells. These daughter cells have the same characteristics as like stem cells.
2. Unique ability to direct tumor heterogeneity as well as tumor survival: CSCs can differentiate into various cancer cell lineages, also assist the growth of the tumor cell along with survival.
3. High tumorigenic potential: CSCs have the capability to swiftly proliferate and form non-CSC linages with a new tumor cell.

Different researches (in vivo and in vitro) have been shown that the cancer cells originated from a similar tumor have distinguished features to generate malignant tumor spheroid. Accumulation of genetic and epigenetic modifications in the same tumor derived from cancer cells possesses diverse signaling and cellular properties. These alterations in tumor assets are related to heterogeneity and the plasticity of CSCs that can be identified with certain specialized biomarkers [126].

### 10.5.2 Natural Compounds and Lung Cancer Stem Cells

Lung malignant growth has been known as a perilous disease from several years. In comparison to other cancers, the expiry rate of such cancer is more




ALDH: Aldehyde dehydrogenase; ALDH1A1: aldehyde dehydrogenase 1 A1; CD133: Antigen; Nanog: Transcription factor; Oct-4: octamer-binding transcription factor 4; SOX-2: Sex determining region Y box 2; CD44: Non-kinase transmembrane glycoprotein; 1ABCG2: Biomarker

**Fig. 10.6** Natural compounds targeting lung cancer stem cells

[127]. Therapeutic approaches such as surgery, targeted therapy, chemotherapy, and radiotherapy have failed to get rid of the CSCs population which is the main source of disease relapse. Thus, natural compounds have been found as a therapeutic intervention that specifically targets CSCs in an efficient and precise way to eliminate lung cancer (Fig. 10.6).

#### 10.5.2.1 Chrysotoxine

Chrysotoxine (bibenzyl) is derived from the stem of *Dendrobium pulchellum* and is reported to inhibit metastasis and sensitize anoikis in lung cancer cells via an anchorage-independent manner. Recently, the suppressive role of chrysotoxine was investigated in primary CSCs culture and cell lines H23 and H460 (CSC-rich population). Chrysotoxine has the ability to decrease CSC markers such as CD44,

CD133, ALDH1A, 1ABCG2, and inhibited CSC-like phenotypes through the Src-AKT-Sox2-dependent mechanism [128].

#### 10.5.2.2 Vanillin

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is isolated from *Vanilla planifolia* (seed) and extensively used as a flavoring agent in cosmetics and food. Vanillin induced apoptosis and inhibited angiogenesis, lamellipodia formation, and cell migration in various types of cancer including lung cancer. Additionally, vanillin reduces ALDH1A1 and CD133 expression and associated transcription factor Nanog and Oct4 in H460 cells via reducing Akt and down streaming CSC transcription factors [129, 130].

#### 10.5.2.3 Silibinin

Silibinin, a polyphenolic flavonoid isolated from *Silybum marianum* (milk thistle seed), has the ability to diminish lung cancer. Silibinin abridged aldehyde dehydrogenase (ALDH) expressing CSC-like cells and also prevented the formation of lung cancer spheres in a dose-dependent manner in erlotinib refractory cell populations [131].

#### 10.5.2.4 Salinomycin

Salinomycin, a polyether ionophore antibiotic is obtained from *Streptomyces albus*. Salinomycin treatment has shown to inhibit tumor-sphere formation as well as reduce Oct-4, SOX2, and Nanog expression in aldehyde dehydrogenase A549 lung cells [132]. Both salinomycin-NPs (salinomycin-nanoparticles) and salinomycin have been found to target CSC biomarker CD133 and reduce tumor-sphere formation. Moreover, a combination of gefitinib-NPs and salinomycin-NPs was reported to have an efficient suppressive impact against the growth of tumors than single gefitinib-NPs or salinomycin-NPs or combination of salinomycin and gefitinib [133, 134].

## 10.6 Conclusion

Cancer is caused by uncontrolled proliferation and growth of cells. Lung cancer is a common type of cancer and is considered the leading cause of mortality throughout the world. Since chemotherapeutic drugs act as an efficient approach for lung cancer treatment, but cancer cells have the potential to exhibit resistance against chemotherapy. Although radiation and immunotherapy are also reported as therapeutic interventions to eradicate cancer cells proliferation and progression, but not exhibit promising treatment approaches. In this regard, molecular targeted therapy of natural compounds with fewer or no side effects has been found as an efficient and alternative treatment strategy for lung cancer. Phytochemicals such as curcumin, quercetin, berberine, resveratrol, gigantol, and indole-3 carbinol are reported to inhibit apoptosis via cell cycle arrest, upregulation of Bax, Bad, and downregulation of anti-apoptotic proteins such as Bcl-2, XIAP, and Bcl-xL. Moreover, this chapter also

highlighted that these natural compounds have also the ability to target intracellular signaling pathways such as PI3K/Akt, ERK1/2, NFκB, and TGF-β1 mediated pathways to inhibit the growth of tumor cell. Conclusively, natural compounds could serve as an ideal anticancer drug for the treatment of lung cancer by regulating the molecular targets involved in apoptosis, angiogenesis, and metastasis of tumor cells.

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