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Minnatallah Al-Yozbaki[a], Peter J. Wilkin[a, b], Girish Kumar Gupta[c, d] and Cornelia M. Wilson[a, c]

[a] Canterbury Christ Church University, School of Human and Life Sciences, Life Sciences Industry Liaison Lab, Sandwich, UK
[b] Peter Wilkins Organics, Canterbury, UK.
[c] Department of Pharmaceutical Chemistry, Sri Sai College of Pharmacy, Sri Sai Group of Institutes, Badhani, Pathankot, Punjab, India.
[d] Novel Global Community Educational Foundation, Australia.

TEL: +44 (0)1304 906 806

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Abstract

Lung cancer is a leading cause of cancer deaths worldwide. The management of lung cancer treatment is often ineffective as a result of the development of drug resistance, reactions to treatment, drug-drug interactions or non-specific targeting of the anti-cancer drugs. Natural compounds show promise and potential activity in lung cancer with very few side effects. While, the combinatorial action of an anti-cancer drug with a natural compound provide synergistic action which help to boost the overall therapeutic action against cancer cells. In cancer, there is a dysregulation of apoptosis which facilitates the cancer cell to survive resulting in progression of the cancer. Many cancer drugs cause mutations of genes that regulate the cancer which should kill the cancer cell but lead to chemoresistance. There are many natural compounds that could specifically target different cell signalling pathways associated with cancer progression to provide a cytotoxic effect in the target cell. The importance of these compounds is emerging in many therapies developed with dual action often including a natural compound. In this review, we present a selection of these natural compounds and how they target lung cancer cells with a focus on the cell signalling pathways. Further work is required to delineate the potential action of natural compounds in the treatment against cancer.

Abbreviations

ADK, adenocarcinoma; DR4, death receptor 4; EGFR, epidermal growth factor receptor; FAK, focal adhesion kinase; KRAS, Kristen Rat Sarcoma viral oncogene; LBK1, Serine/Threonine-Protein Kinase; LCC, large cell carcinoma; MEKK, Mitogen-activated protein/ERK kinase kinase; MMP-2, -9, matrix metalloproteinase-2 and -9; NSCLC; non-small cell lung cancer; PCNA, proliferating cell nuclear antigen; PKC, protein kinase C; phospholipase C gamma, PLCγ; SCC, squamous cell carcinoma ; SCLC, small-cell lung cancer; TKI, tyrosine kinase inhibitor; TP53, tumour protein p53; VEGFR1/2, vascular endothelial growth factor receptor 1/2.

Introduction

Lung cancer is the leading cause of 18.6% of total cancer deaths worldwide. Small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are the two major lung cancer groups based on histological classification; NSCLC represents 80% of all lung cancer cases and subdivided into adenocarcinoma (ADK) squamous cell carcinoma (SCC) and large cell carcinoma (LCC). Tobacco smoking is the most common lung cancer's risk factor; other risk factors such as environmental, hormonal, genetic factors also play a role in lung cancer development. ADK is the most common type of all lung cancers, derived from the epithelial line of small peripheral airways. It is more common in non-smokers; smokers can also develop ADK. Different genetic mutations such as p53, epidermal growth factor receptor (EGFR), Kristen Rat Sarcoma viral oncogene (KRAS), and Serine/Threonine-Protein Kinase (LBK1) are involved in this type of lung cancer. Gefitinib and erlotinib target EGFR mutation and is used for the treatment of metastatic NSCLC patients. While SCC is more common in smokers. It is located along the major pathways in the central part of the lung. EGFR mutation is absent in this type and the agents used to target this mutation are ineffective against SCC. LCC is the undifferentiated subtype of NSCLC and only diagnosed by surgical specimens. On the other hand, SCLC is the aggressive type of lung cancer with early developed metastasis, RB1 and TP53 genes mutations are more seen in this type than NSCLC. Treatment of lung cancer is difficult due to adverse reactions, drug resistance and the specificity of certain drugs. Natural compounds represent an interesting approach for lung cancer therapy with potential to be effective and have few side effects. Natural compounds come from various sources, including microorganisms, plants, and animals which provide an interesting drug discovery avenue of cancer therapeutics [1]. Natural compounds are present in a variety of plants and have been studied since ancient times. Many of plants and their active phytochemicals have been shown to have anti-cancer activity [2]. There are approximately 250,000 different plant species with

just over 25,000 which have been investigated as possible therapies of disease. The phytochemicals and other similar analogues originate from different parts of plants such as the seeds, stems, roots, flowers, and bark. The main phytochemicals found in plants to have activity against cancer cells are flavonoids, terpenes, taxanes, alkaloids, lignans, saponins, oils, gums, glycosides, minerals, and vitamins (Table 1). Natural compounds are regarded to possess chemotherapeutic activity and have the potential to be used in the treatment of cancer [3]. Even metabolites, alpysinones from a sponge called Aplysina geradogree have demonstrated to have anticancer activity in human cancer cell lines [4]. These products have been demonstrated to act on various cell signalling pathways such as PI3K, MAPK/ERK, Akt, mTOR and proteins that activate cancer such as COX-2, CDK4 kinases, Cdc2, Bcl-2, and MMP. In addition, the phytochemicals have been shown to activate processes such as DNA repair through p21, p51, and p53; and stimulate enzymes involved in cellular protection such as the caspase family (caspase 3, 7, 8, 9, 10 and 12).

Apoptosis is a form of programmed cell death initiated by signal transduction events allowing the control of cellular homeostasis and cell death [5]. In the case of cancer, cells are transformed and become immortal and difficult to remove through these normal pathways. Apoptosis can be divided into intrinsic or extrinsic according to the trigger of cell death. Different studies have examined the effect of the natural compounds on all the lung cancer types and found that some inhibit the cell proliferation and/or induce apoptosis through different pathways such as p53 activation pathway or by an extrinsic and intrinsic pathways via the death receptor and mitochondria, while other inhibits metastasis and angiogenesis via blocking the tyrosine kinase receptors and prevent downstream pathways and VEGFR1/2, respectively. Another mechanism of cancer cell death is the action of chemotherapy on the autophagy pathway, which involves the lysosome fusing with the autophagosome facilitating self-degradation of intracellular proteins and organelles. This pathway is regulated by beclin

and ATG5 in the absence of apoptotic factors [6, 7]. In this review, we explore the role of different natural compounds and their effects on the cancer cell with a focus on lung cancer, the cell signalling pathways, apoptosis, angiogenesis and metastasis.

Classification of natural compounds

Plants provide an array of natural compounds that potentially could be used for drug discovery of a number of diseases, including cancer. Here we will discuss the different classes of phytochemicals found in plants that demonstrate potential activity against cancer.

Alkaloids

Alkaloids are a broad class of compounds found in the kingdom of plants and are considered the most active against different cancers [8]. The structure of alkaloids normally has a nitrogen atom within a heterocyclic ring with low toxicity [9] (see Figure 1). Alkaloids have been demonstrated to have a number of functions such as anti-microbial, anti-inflammatory and anti-cancer [10-12]. There are some well-developed anti-cancer drugs that are synthetic alkaloid derivatives such as vinorelbine, vinblastine, vindesine and vincristine (Table 2). These are examples of drugs that have been approved in Europe and the US [13].

Vinblastine is known as an anti-mitotic drug and was discovered in the periwinkle plant called *Catharanthus roseus.* The mechanism of action of this drug causes a disruption of the microtubule function leading to shortening the microtubules and reduction of the mitotic spindle which directly impacts on cellular proliferation [14]. *In-vitro* studies on cancer cells with low doses of vinblastine reduces or prevents mitosis. In the clinic, vinblastine is highly

potent and demonstrates 65% five-year survival rate in patients with refractory anaplastic large-cell lymphoma (ALCL) [15].

Flavonoids

Flavonoids are produced as plant metabolites, found in many fruits, vegetables and some beverages. They contribute to the colour, flavour of foods and possess pharmacological activity [16]. Flavonoids have a polyphenolic structure consisting of a 16-carbon skeleton and structures surrounding a heterocyclic oxygen ring [17] (see Figure 2). A number of studies have shown that flavonoids can affect a number of biological processes causing cell cycle arrest and cell apoptosis, blocking cell proliferation and angiogenesis and preventing multi-drug resistance [17]. Flavonoids are also potent inhibitors of enzymes such as cyclo-oxygenase (COX), xanthine oxidase, phosphoinositide 3-kinase and lipoxygenase [18-20].

Saponins

Saponins are commonly found in plants (roots, leaves, seeds etc.) as well as in animals. The structure of saponins have various carbon skeletons, and they are classified into two groups, steroids or triterpenes (Figure 3). They have a glycone part composed of oligosaccharides in a linear or branched form which is attached to hydroxyl groups via acetal linkage [21]. Saponins have been shown to cause cell cycle arrest and apoptosis in cancer cells [22].

Lung cancer

Lung cancer is the most common leading cause of cancer deaths with an incidence of 11.6% of total new cases and 18.6% of total cancer deaths worldwide in 2018 [23]. It is the most commonly diagnosed and leading cause of cancer deaths in male followed by prostate and colorectal cancer, whereas in female breast cancer is the most common cancer followed by

colorectal and lung cancer [23]. Lung cancer divided into non-small cell carcinoma (NSCLC) which accounts 80% of all lung cancer cases and small cell lung carcinoma (SCLC) with 20% of all cases [24]. According to the World Health Organisation (WHO), NSCLC is histologically divided into adenocarcinoma (ADK) (40-50%), squamous cell carcinoma (SCC) (30-35%) and large cell carcinoma (LCC) (5-10%) [24, 25].

The most major risk factor for developing lung cancer is tobacco smoking, while other environmental risk factors include ionising radiation, occupational exposure (asbestos, silica, polycyclic aromatic hydrocarbon, and diesel exhaust), and air pollution; hormonal factors (oestrogen and progesterone); and genetic risk factors (positive family history and genetic polymorphisms) [26].

Lung adenocarcinoma (ADK)

ADK is the subtype of NSCLC, and the most common of all lung cancer types that derived from small peripheral airways epithelial line [27]; and recognised with glandular differentiation or production of mucin. Pneumocytic markers usually expressed in lung ADK along with 80% of lung ADK cases express the Thyroid transcription factor and Napsin A markers [28, 29]. Lung ADK is the common type of lung cancer in non-smokers, compared to smokers who develop all the lung cancer types. Smokers develop ADK in both central and peripheral airways, while ADK occurs in peripheral airways in non-smokers [30]. Genetic mutations that involved in lung ADK are mutations of p53 (50-70%), EGFR kinase domain (10-40%), KRAS (10%-30%), and LBK1 (34%) [31, 32].

The most frequently inactivated tumour suppressor gene is *TP53* which is located on chromosome 17p13 and encodes a nuclear phosphoprotein that is responsible for identifying and binding DNA damaged regions; also controls various genes expression as a transcription factor. However, activation of *TP53* by DNA damage or carcinogenic stress causes cell cycle

arrest through cyclin-dependent kinase inhibitors that are required for DNA repair or apoptosis, and inactivation of *TP53* is the most common genetic defects in lung cancer [33, 34]. KRAS and EGFR mutations rarely occur in the same tumour [35]. KRAS mutation can be found in early-stage lung ADK smoker patients, whereas EGFR kinase mutation is common in lung ADK non-smoker patients [35, 36].

Identification of mutations that drive lung ADK has led to the development of targeted therapies, such as first-generation EGFR tyrosine kinase inhibitors (TKIs) Gefitinib that is used for the treatment of metastatic NSCLC patients with EGFR kinase domain mutation [37], also erlotinib that improves the survival compared to placebo when given to previously treated NSCLC patients express EGFR or high number of copies of EGFR [38]. In contrast to date, there is no specific treatment that could target KRAS mutation for lung ADK patients [39]. Therefore, a number of studies mentioned the role of natural compounds that have anti-cancer and chemoprotective effects on lung ADK through different signalling pathways [27]. Examples of natural compounds are pterostilbene which is derived from *Vitis vinifera* leaves and fruits (blueberries and cranberries) and has an apoptotic effect along with reduction in EGFR expression [40]; β-escin (*Aesculus hippocastanum)* causes cell cycle arrest and increase the p21 expression while decrease the level of proliferating cell nuclear antigen (PCNA) and also reduce the number of tumours in mouse model [41]*;* while *Curcumin (Curcuma longa)* inhibits Stat-3 pathway's activation, leading to cell proliferation reduction [42].

Squamous Cell Carcinoma (SCC)

SCC accounts for ~20% of all NSCLC and occurs because of bronchial epithelium transformation caused by cigarette smoking [43]. Due to the change in smoking behaviours, the incidence of SCC has declined. SCC located in the centre part of the lung along major pathways and cavities can be formed when the tumour reaches a critical size [44]. Metastasis

is less frequent with this type of NSCLC compared to lung ADK; also, EGFR mutations and anaplastic lymphoma kinase (ALK) fusions are absent in this type of cancer and agents that target these mutations are ineffective against SCC [43]. Common mutations that arise in lung SCC are those that are found in histone-lysine N-methyltransferase 2D (MLL-2), cyclin-dependent kinase 2A (CDKN2A), nuclear factor erythroid 2 like2 (NFE2L2), Kelch-like ECH-associated protein 1(KEAP1) as listed by Genome Atlas Research Network 2012 [45]. Along with TP53 and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) alterations [36]. Examples of the natural compounds that have effects against lung SCC [27], including Honokiol that isolated from Mangolia tree's bark studied by Pan and colleagues and found that Honokiol inhibits the tumour growth by interrupting the function of mitochondria and induces apoptosis by rising the cleaved caspase-3 level [46]. While Emodin from the roots and rhizomes Rheum palmatum L. inhibited SK-MES-1 cell line proliferation by ERCC1 and Rad51 downregulation [47].

Large cell carcinoma (LCC)

LCC is a subtype of lung cancer that have undifferentiated features of SCLC, ADK, SCC [48], accounts for 3-9% of all primary pulmonary malignancies and can only be diagnosed by surgical specimens [49]. It consists of round to polygonal sheets of cells that have prominent nucleoli and cytoplasm of pale stain without any gland or mucin formation as seen in ADK, or keratinisation of intercellular bridges as in SCC [50]. Different studies showed the effect of natural compounds on LCC; Wei's group used different lung cancer cell lines including NCI-H460 which is large cell lung cancer cell and studied the anti-cancer effect of dioscin and found that dioscin inhibited the proliferation of these cells through activation of caspases-3 and -9 that lead to apoptosis, Bcl-2 and Bcl-xl expression's downregulation, Bax, Bak, and Bid upregulation and S phase cell cycle arrest [51]. Another group used α-Tomatine (*Lycopersicon*

esculentum Linn.) which is steroidal glycoalkaloid in immature green tomatoes to study the anti-metastatic effect in NCI-H460 and the results showed that α-tomatine significantly inhibit the NCI-H460 cells adhesion, invasion, and migration in a dose-dependent manner. Also, inhibit the focal adhesion kinase (FAK) and phosphatidylinositol 3-kinase (PI3K)/Akt signalling pathway [52]. Didymin which is the dietary flavonoid glycoside from citrus fruits has anti-proliferative activity on H460 and A549 NSCLC and induce apoptosis without affecting the cell cycle but suggested that through Fas/Fas apoptotic ligand system [53].

Small cell lung cancer (SCLC)

SCLC is an aggressive neuroendocrine tumour, characterised by high growth fraction, short doubling time, and widespread metastasis that develops early [54]. It accounts for about 12% of all new cases and 13% of all newly diagnosed cases of lung cancer globally. Approximately, +90% of SCLC patient are current, or past heavy smokers and the risk increases with the duration and smoking intensity [55]. About 90% of cases are positive for thyroid transcription factor-1, cytokeratins which is one of the epithelial markers also seen in many SCLC tumours. Loss of tumour-suppressor retinoblastoma gene *RB1* and more frequent mutations in *TP53* seen in SCLC than in NSCLC [55]. The active component of turmeric (Curcumin) had been studied by Yang group for anti-tumour mechanisms on SCLC and found that curcumin inhibits the STAT3 phosphorylation and thus downregulate its downstream targets that lead to suppression of cell proliferation, cell migration and invasion [56]. A study by LV and colleagues found that Wentilactone A which is one of the tetranorditerpenoids that is isolated from *Aspergillus wentii* EN-48 (endophytic fungus isolated from an unknown species of marine brown algae) has a significant proliferation inhibition effect on large cell lung cancer (NCI-H460) and small cell lung cancer (NCI-H446) through targeting Ras/Raf/ERK pathway that activates apoptosis and initiates cell cycle arrest at G2/M phase, and *in vivo*, they found it is effective in inhibiting the

growth of tumour xenograft and safer than cisplatin [57]. SCLC cell lines NCI-H446 and NCI-H1688 were used to study the effect of evodiamine (EVO) which is a major quinazolinecarboline alkaloid in *Evodia rutaecarpa* on cell growth, apoptosis and cell cycle arrest. On dose and time- dependent manners, they found that EVO induces apoptosis by intrinsic caspase-dependent pathways, cell cycle arrest, and it represents the promising drug candidate that has anti-tumour effect for SCLC [58].

Natural compounds that induce apoptosis in lung cancer

Apoptosis is a programmed cell death that is important in both physiological and pathological conditions, derived from a Greek word that means dropping off. Apoptosis is mediated through three pathways, the intrinsic (mitochondrial) pathway, extrinsic (death receptor), and intrinsic endoplasmic reticulum pathway (Figure 4). Reduction in apoptosis or its resistance has a role in carcinogenesis through various mechanisms including caspase function reduction, impaired signalling of the death receptor, and disruption of pro-apoptotic and anti-apoptotic proteins balance [59].

A study showed the anti-tumour effects of three extracts of Thai herbs on A549 cells, these extracts are ethyl acetate extracts of *Bridelia ovata* (BEA), *Croton oblongifolius* (CEA), and *Erythrophleum succirubrum* (EEA), and an ethanolic extract of E. succirubrum (EE) showed apoptotic effect through induction of mitochondria-mediated pathway and also a synergistic effect when these BEA combined with methotrexate and EE with methotrexate and etoposide [60]. Another study found that a flavonoid compound known as acacetin inhibits cell proliferation and induces apoptosis and cell cycle arrest by increasing the expression of p53 and p21/WAF1 protein, also enhances Fas and two forms of Fas ligands leading to initiation of apoptosis in A549 cells [61] (Figure 4). Gomathinayagam and colleagues examined the anti-cancer effect of Plumbagin (*Plumabago zeylanica*) on H460 and A549 lung cancer cells and

found that Plumbagin sensitises H460 more than A549 cells and has apoptotic effect in H460 by causing cell cycle arrest in the G2/M phase with a modulating effect on pro-apoptotic and pro-survival factors in addition to its effect on Akt signalling that mediated by EGFR [62]. Proscillaridin A, a constituent of squill-Drimia maritima has anti-cancer effect in A549 and H1975 NSCLC cell lines [63] and induces apoptosis in EGFR mutant cell lines through activation of caspases 3, 7, and 9, inhibition of Akt, upregulation of pro-apoptotic Bax, and downregulation of anti-apoptotic protein Bcl-2; in addition to its inhibition effect on Na+/K+ ATPase that contributes to the cytotoxic effect in the cancer cells. Also, it increases the expression of death receptor 4 (DR4) and downregulates NF–κB [64]. A study by Hessien's group found that dose-dependent treatment of H460 cells with green tea and ginger polyphenolic extracts inhibits the cells proliferation and induces apoptosis by increasing p53 and decreases Bcl-2 proteins levels in the treated cells compared to control [65]. A549 human NSCLC cells used in this study to investigate the effect of xanthohumol which is a natural compound of the female hop plant (*Humulus lupulus*) on cell apoptosis by increasing the activity of caspase -3, -8 and -9 and arresting the cell cyle on phase S [66] (Figure 4). Several natural compounds inhibit the tumour cells growth by targeting one or more of the intermediates involved in various signalling pathways and lead to induction of apoptosis which represents the important target in preventing cancer development.

Natural compounds that inhibit metastasis and angiogenesis

One of the factors that contribute to tumour progression and spread is the angiogenesis which involves new blood vessels growth from the pre-existing vessels [67]. The key factor for angiogenesis is known as vascular endothelial growth factor (VEGF) family which consist of five glycoproteins VEGFA, VEGFB, VEGFC, VEGFD, and placental growth factor (PIGF) and interact with three receptor tyrosine kinases VEGFR1 (VEGF receptor 1), VEGFR2, and

VEGFR3. Upon ligand binding, VEGFRs stimulate different downstream signalling pathways, such as in case of VEGFR2 are phosphotidylinositol-3 kinase (PI3K)/Akt, mitogen-activated kinases, the nonreceptor tyrosine kinase Src, and PLCγ (phospholipase C gamma)/PKC (protein kinase C) which involved in angiogenesis, vascular permeability, and vascular homeostasis [68].

Marmesin which is a natural coumarin compound isolated from *Broussonetia kazinoki* was studied in NSCLC and was demonstrated to have anti-tumour effects by blocking mitogen-stimulated cell invasion and downregulating VEGFR2 and matrix metalloproteinases -2, also inhibits the formation of new vessels in human umbilical vein endothelial cells by suppressing the expression and secretion of VEGF in NSCLC, thus affects migration, invasion and angiogenesis [69] (Figure 4).

On the other hand, metastasis is the spread of cancerous cells from the initial site to distant tissues and organs. It is responsible for the death of most patients suffering from cancer. Metastasis cascade which involves three main processes: invasion, intravasation, and extravasation; cell-cell and cell-matrix adhesion changes are important during metastatic cascade [70]. A study found that using curcumin (diferuloylmethane), which is a natural compound isolated from *Curcuma longa* could inhibit the migration and invasiveness of A549 cells by blocking of adiponectin receptor 1 through NF-κB/MMP pathways [71]. Also, another study showed that curcumin inhibits A549 migration and invasion via Mitogen-activated protein/ERK kinase kinase (MEKK) and extracellular-signal-regulated kinase (ERK) pathways that resulted in matrix metalloproteinase-2 and -9 (MMP-2, -9) inhibition [72] (Figure 4). In addition to its inhibitory effect on MMP-2 and -9, curcumin could inhibit lung cancer cells migration and invasion induced by EGF or TGF- β1 *in vitro,* and this is related to Rac1/PAK1 signalling pathway inhibition in which Rac1 is small Rho GTPase family protein plays a role in cytoskeleton arrangement by activating its effector PAK1 [73]. A study showed that apigenin

which is a flavonoid found in fruits and vegetables inhibits cell proliferation, invasion, and metastasis of A549 human lung cancer cells through its inhibiting effect on the phosphorylation of Akt in a dose and time dependant manner [74]. Metastasis and angiogenesis are crucial steps for cancer spread and inhibition of these steps by using different natural compounds that are available for human use could pave the way for promising strategies to prevent cancer progression.

Current challenges of natural compounds in lung cancer treatment.

Natural product research is a strong way to discover biologically active compounds that have unique structures and mechanism of actions [75]. Different natural compounds are being studied for their preventive and therapeutic effects, such as polyphenols and bioactive compounds derived from plants. Many vegetables and spices have anti-inflammatory and antioxidant properties, others like alkaloids, flavonoids, curcumin, berberine, and many others have been tested *in vitro* and *in vivo* and introduced as cancer complementary therapy due to their anti-proliferative and pro-apoptotic effects that they have. The difficulties that restrict their use in clinical practice are their poor bioavailability and toxicity. Curcumin and berberine show poor water solubility thus, different carriers are required to improve their bioavailability and facilitate their delivery across cell membranes [76]. However, there are several opportunities to develop novel analogues and prodrugs from well-established drug classes like vinca alkaloids and taxanes having superior clinical efficacy and low toxicity, in addition to new administration methods. Combination of synthetic chemotherapeutic drugs or monoclonal antibodies with cytotoxic natural products is another promising approach to provide effective chemotherapeutic agents [75]. Currently, there are many natural compounds or their derivatives in combination with synthetic drugs at different stages of clinical trial for lung

cancer (Table 3). Thus, this offers some promise in developing alternative treatments for lung cancer.

Conclusion

The current challenges in the cancer field are being able to diagnose cancer at an early stage and providing effective treatment. These therapeutic approaches often fail as a result of genomic changes or mutations in genes driving cancer. Current cancer treatment causes many side effects with a need to improve effective cancer therapy. There is a growing interest in the development of alternative therapies that could provide effective treatment with fewer side effects. It is evident from many studies that natural compounds could provide a promising and effective therapeutic route for lung cancer treatment. Herein, this review provides a glimpse into possible medicinal routes using natural compounds in lung cancer and their mechanisms of action. Natural compounds provide a potential solution while the effectiveness of their action against cancer still requires further research and commitment from the pharmaceutical industry.

Figure legends

Figure 1 Chemical structure of Alkaloids

Figure 2 Chemical structure of Flavonoids

Figure 3 Chemical structure of Saponins

Figure 4 Signalling pathways of natural compounds in lung cancer

Different signalling pathways of natural compounds in lung cancer. Apoptotic pathway is mediated through extrinsic (death receptor), intrinsic (mitochondria), and also by p53/p21 activation that results in cell cycle arrest. Inhibition of angiogenesis is by blocking the interaction of VEGF with VGEFR1/2 and thus terminates the downstream PI3K/Akt, MEK, and Src/FAK pathways. Metastasis is prevented by inhibiting MMP-2,-9 activation, cell survival by PI3K/Akt, and actin cytoskeleton reorganisation.

Table 1 List of plants and their phytochemicals with potential against lung cancer.

Table 2 Approved natural compounds for lung cancer.

Table 3 Natural compounds in clinical trials for lung cancer.

Plant species	Plant part	Phytochemical	Ref
Vitis vinifera	Leaves, fruit	Pterostilbene	[40]
Aesculus hippocastanum	Seeds	Beta-Escin	[41]
Curcuma longa	Rhizomes	Curcumin	[42]
Rheum palmatum	Roots, rhizomes	Emodin	[47]
Dioscorea nipponica Makino	Rhizomes	Dioscin	[51]
Lycopersicon esculentum Linn.	Fruits	alpha-Tomatine	[52]
Citrus X sinensis	Fruits	Didymin	[53]
Aspergillus wentii	Fungus	Wentilactone A	[57]
Evodia rutaecarpa	Fruit	Evodiamine	[58]
Camelia sinesis	Leaves	Epicatechingallate	[77]
Ziziphus spina-christ	Leaves, flowers	Doxorubicin, spinanine-A, Rutlin, Quercetin	[78]
Sylibum marianum	Flower, leaves	Silibinin	[79]
Oldenlandia diffusa	Stem bark, leaves,fruit peel	Ursolic acid	[80]
Psoralea corylifolia	Seeds	Corylfolinin, Psoralen, Bavachinin	[81]
Panax ginseng	Leaves	Panaxatriol, Panaxadiol	[82]
C. roseus	Leaves	Vinblastine, Vincristine	[83]
Moringa oleifera	Seed	Pterygospermin 4-(40-O-acetyl-a-L-rhamnopyranosyloxy), 4-benzylisothiocyanate, benzylisothiocyanate	[84]
Catharanthus roseus	Bark, leaves	Vindesine	[85]
Capsicum annuum	Fruit	Capsiacin	[86]
Allium cepa (plus various fruits and vegetables)	Fruit	Fisetin	[87]
Tripterygium wilfordii	Root	Celastrol	[88]
Tabernaemontana divaricata	Leaves	Conophylline	[89]
Bleekeria vitensis	Stem, bark, leaves, root	Ellipticine	[90]
Camptotheca acuminata	Wood	Topotecan	[91]
Delphinium	Fruit & vegetables	Delphinidin	[92]
Humulus lupulus	female hop plant	Xanthohumol	[66]
Podophyllum peltatum	Rhizome Picropodophyllin	Picropodophyllin	[93]
Saussurea lappa	Roots	Costunolide	[94]

Table 1 List of plants and their phytochemicals with potential against lung cancer.

Generic name	Origin	Mechanism of Action	Reference
Paclitaxel	Bark of the Pacific Yew, Taxus brevifolia Nutt. (Taxacea)	anti-mitotic drug	[95]
Docetaxel	Bark of the Pacific Yew, Taxus brevifolia Nutt. (Taxacea)	anti-mitotic drug inhibiting microtubule depolymerisation	[96]
Vinblastine and vincristine	Madagascar periwinkle, Catharanthus roseus G. Don. (Apo-cynaceae)	aggregates tubulin and leads to microtubule depolymerisation	[95]
Topotecan and irinotecan	semi-synthetic derivatives of camptothecin	inhibition of topoisomerase II	[95, 97]
Etoposide and Teniposide	semi-synthetic derivatives of epipodophyllotoxin	inhibition of tubulin polymerisation and topoisomerase II	[95, 98]

Table 2 Approved natural compounds for lung cancer.

Drug	Phase	Reference
Carboplatin/Paclitaxel/AZD1775	phase 2	[99]
Nilotinib and Paclitaxel	phase 1	[100]
Curcumin and EGFR-TKIs	phase 1	[101]
Lovaza and Curcumin	phase 2	[102]
Fosbretabulin, Carboplatin, Paclitaxel, and Bevacizumab	phase 2	[103]

Table 3 Natural compounds in clinical trial for lung cancer

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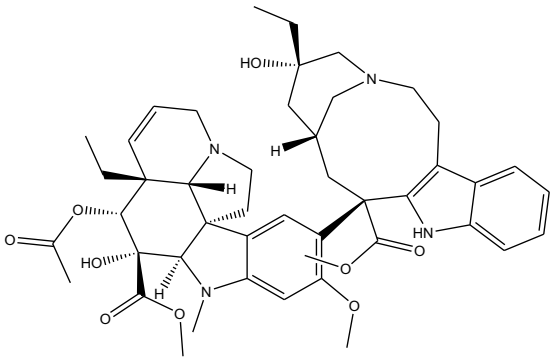
Figure 1



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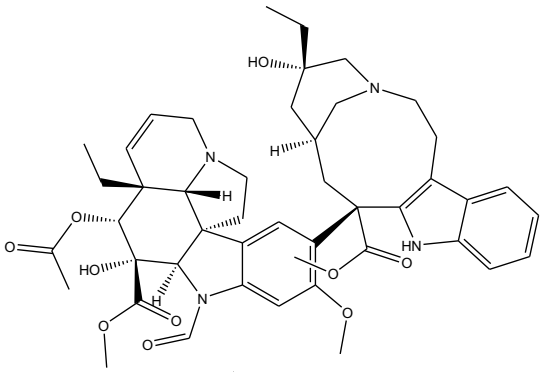

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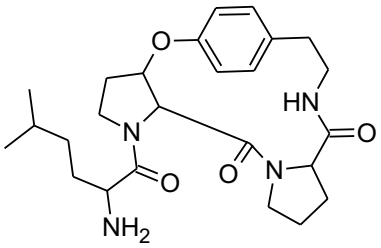
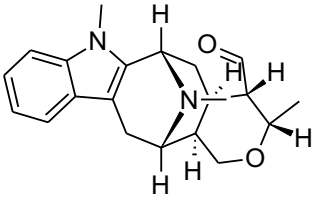


Spinanine-A



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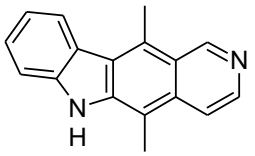
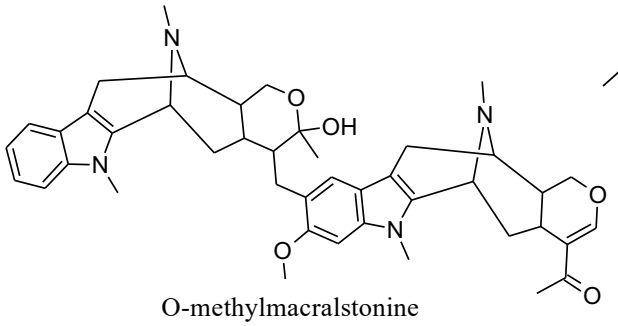
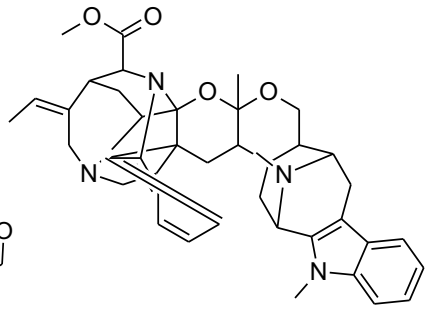


Ellipticine



O-methylmacralstonine



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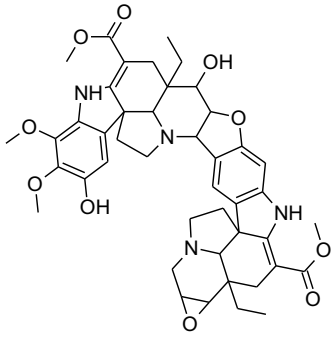

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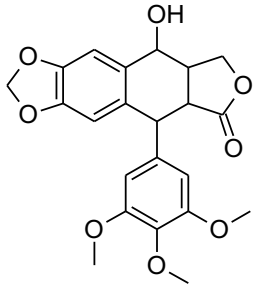

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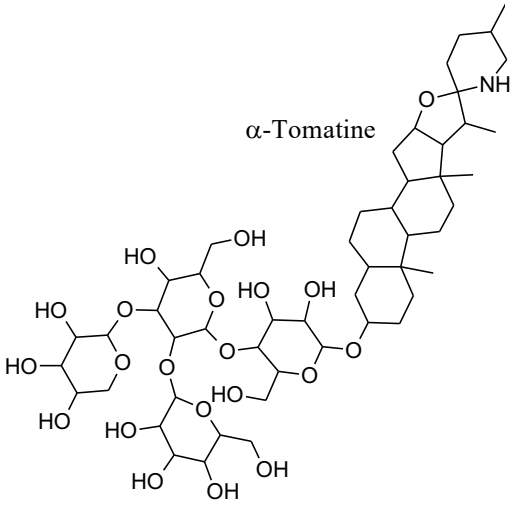
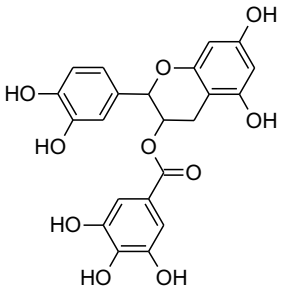
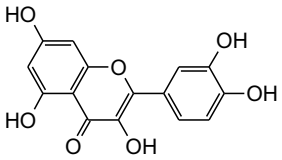


α-Tomatine

Figure 2



Epicatechingallate



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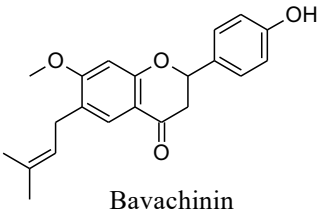
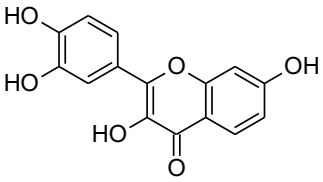
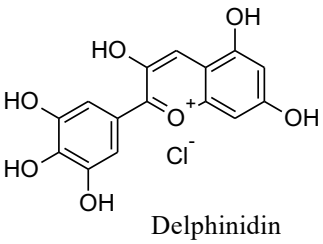


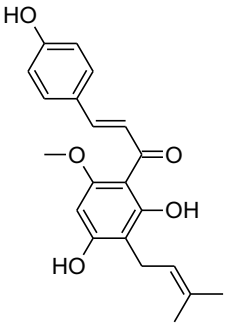
Bavachinin



Fisetin

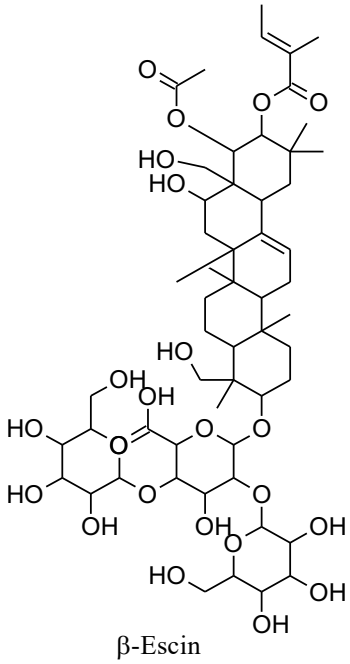


Delphinidin

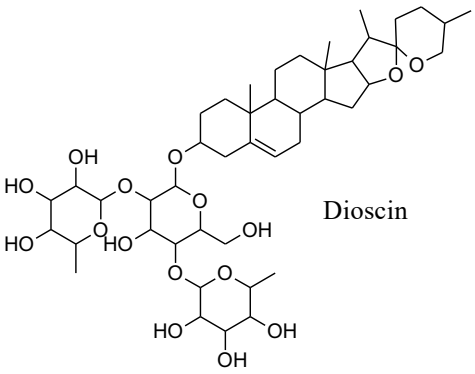


Xanthohumol

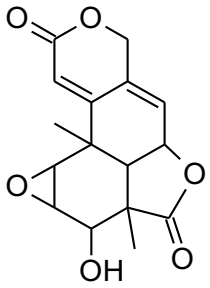
Figure 3



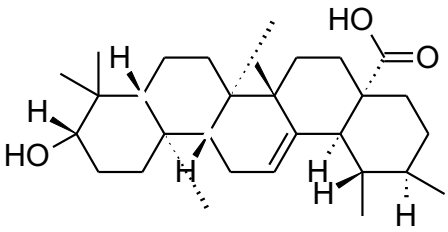
β-Escin



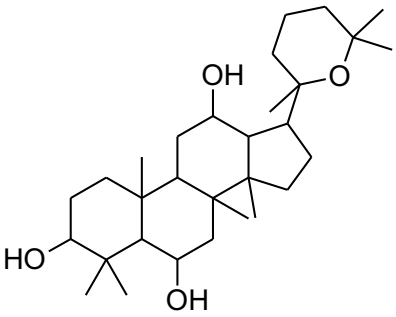
Dioscin



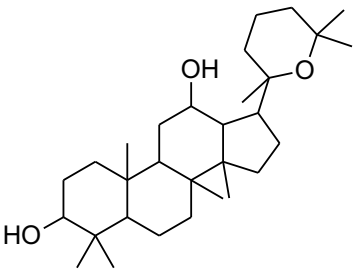
Wentilactone A



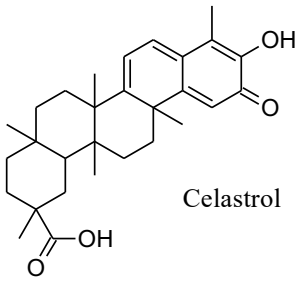
Ursolic acid



Panaxatrol

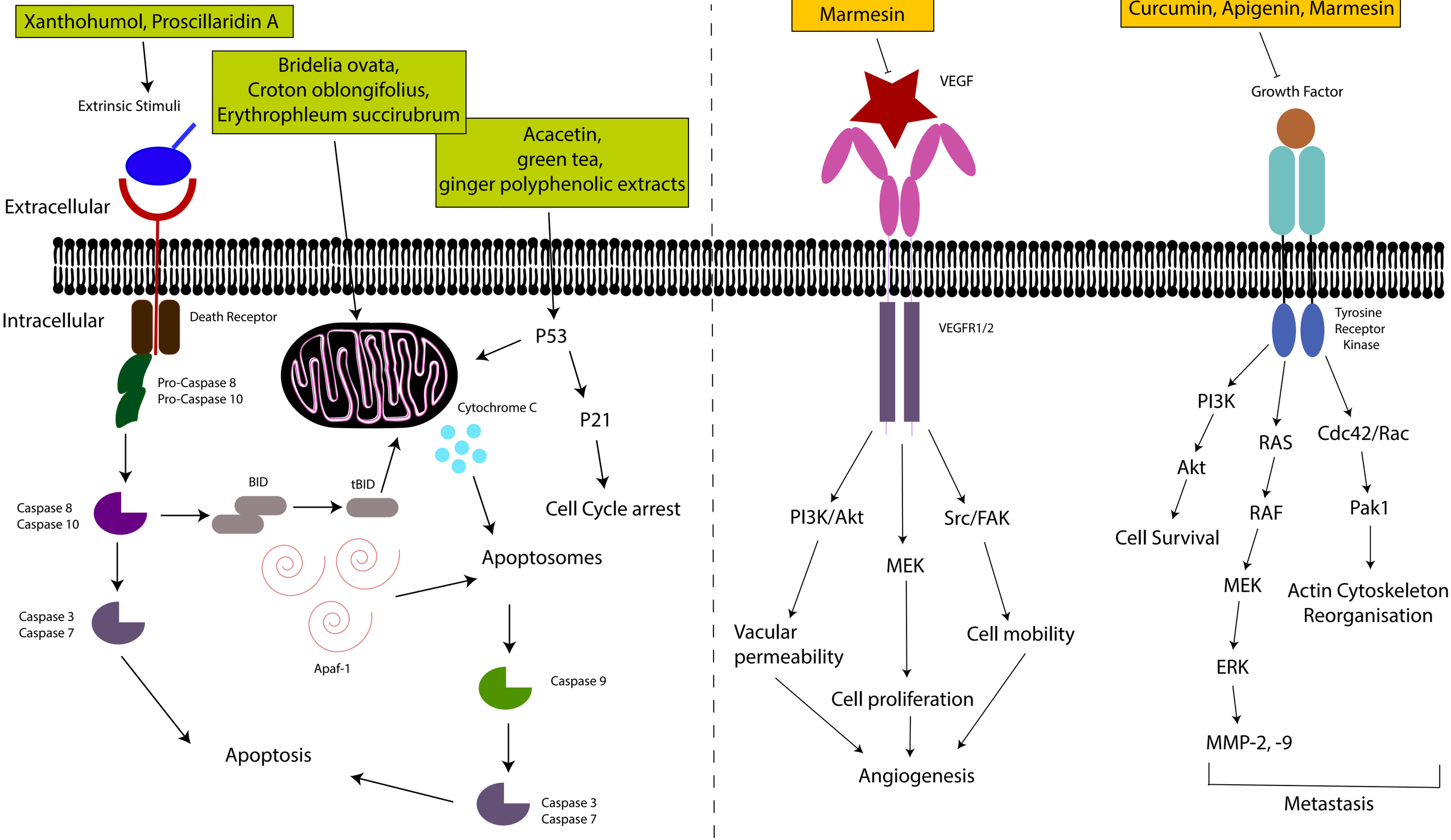


Panaxadiol



Celastrol

Figure 4


Xanthohumol, Proscillaridin A
Extrinsic Stimuli
Bridelia ovata,
Croton oblongifolius,
Erythrophleum succirubrum
Acacetin,
green tea,
ginger polyphenolic extracts
Extracellular
Intracellular
Death Receptor
Pro-Caspase 8
Pro-Caspase 10
P53
Cytochrome C
P21
Cell Cycle arrest
BID
tBID
Caspase 8
Caspase 10
Apoptosomes
Caspase 3
Caspase 7
Apaf-1
Caspase 9
Apoptosis
Caspase 3
Caspase 7
Marmesin
VEGF
VEGFR1/2
PI3K/Akt
MEK
Src/FAK
Vacular
permeability
Cell mobility
Cell proliferation
Angiogenesis
Curcumin, Apigenin, Marmesin
Growth Factor
Tyrosine
Receptor
Kinase
PI3K
RAS
Cdc42/Rac
Akt
RAF
Pak1
Cell Survival
MEK
Actin Cytoskeleton
Reorganisation
ERK
MMP-2, -9
Metastasis