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Herbal Phytoconstitutes: Natural Weapon Against Lung Cancer

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Abstract
By the twenty-first century, lung cancer has become well-known as one of the most frequent cancers. Nowadays, Lung cancer ranks second globally regarding new cases and first globally regarding cancer-related deaths. To fight this spreading; surgical procedures, radiation treatment, chemotherapy or combination of these strategies is commonly used. Thanks to their phytochemical compounds; Many plants have proved their efficacy as anticancer agents by different mechanisms as *Allium sativum*, *Curcuma longa*, *Camellia sinensis* and *Panax ginseng* etc. by Apoptosis, cell cycle arrest, Tyrosine Kinase inhibitors, PI3K/AKT/mTOR inhibitor pathway and Autophagy. In this review article, the effect of using natural plants as anticancer agents and the possibility to use natural plants extracts in combination with chemotherapy to reduce chemotherapy side effects, or to enhance the anticancer activity of chemotherapy, will be examined.

Keywords: Lung cancer; natural plants; anticancer agents; phytochemical compounds.

1. Introduction

Lung cancer is the first reason for death in all types of cancer. Lung cancer has killed around 2 million humans in 2020, and it is now a global public health issue [1]. According to Sung H, *et al* [2], lung cancer remained the most common cause of cancer-related mortality with an anticipated 1.8 million deaths. Lung cancer is the second most frequently diagnosed cancer in women, after breast cancer, and in men, after prostate cancer.[2]. There are no specific reasons for lung cancer but there are risk factors leading to it such as family history, a history of infections, and chronic obstructive pulmonary disease. Smoking increases lung cancer risk five to ten times. The lung cancer risk increases by around 20% in nonsmokers who are exposed to ambient tobacco smoke. Additional recognized environmental risk factors comprise of exposure to diesel, asbestos, radon, and ionizing radiation [3]. Patients with lung cancer can be classified histologically into two groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximately 80% of cases of lung cancer are of the NSCLC type [4].

Treating lung cancer is complicated and could go through different steps in accordance with the patient's condition. Surgery continues to be the most efficient treatment option for individuals with lung cancer, but it also plays an essential role in diagnosis, staging, and treatment. Though aggressive surgery is feasible for about 20–30% of individuals with early-stage NSCLC, only 40–50% of these patients receive a cure [5]. So, the most common way to manage lung cancer is chemotherapy such as the platinum-based medications oxaliplatin, carboplatin, and cisplatin which are frequently used to eliminate cancer through chemotherapy [6]. Systemic chemotherapy remains the principal treatment for both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), notwithstanding the increasing interest in the advancement of non-cytotoxic targeted treatments. [7].

In some cases; chemotherapy may be prescribed after surgery. Individuals with pathologic stage T1-2N0M0 SCLC who received surgical resection only do not perform as patients who receive adjuvant chemotherapy only or chemotherapy in conjunction with cranial radiation [8]. Postoperative radiation has not been demonstrated to boost survival, however adjuvant cisplatin-based chemotherapy did significantly improve the cure rate by 5% [5]. Due to the massive chemotherapy side effects

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experienced in different patients with multiple carcinomas as nausea, vomiting and fatigue [9] and specially in patients with (NSCLC) could experience breathing difficulties, bleeding, and exhaustion [10]. There should be a way to reduce these side effects. Hence, novel strategic approaches to cancer treatment have been tested, for instance the complex therapy of cisplatin and natural compounds [11]. There are many mechanisms regarding lung cancer treatment, most common mechanisms will be discussed in this review.Apoptosis is very common mechanism in treating cancer, it is a type of programmed cell death or self-destructive pathways (self-killing) which determine the turnover of entire cells [12]. Several factors affect the process of apoptosis. Some of these factors will be discussed below. Effector Caspase can regulate apoptosis which are a class of cysteine proteases that play essential roles in apoptotic and inflammatory signaling pathways. Caspase-3 and -7, known as effector caspases, are activated into functional subunits and facilitate the apoptotic pathway by cleaving caspase-activated DNase, which subsequently moves to the nucleus to cleave DNA [13]. Apoptosis might be associated with biochemical cell changes like activation of the effector caspases; caspase-3, caspase-6 and caspase-7 which are cysteine proteases induce cell apoptosis, or like stimulation of catabolic hydrolases which decompose cell macromolecules and DNA, or like mitochondrial outer membrane permeabilization (MOMP) which in turn releases cytochrome c into the cytoplasm and with the impact of pro-caspase-9 (a cysteine proteases apoptosis protein) andapoptotic protease-activating factor1(APAF1) generatethe apoptosome which activates the apoptosis effector protein caspases-3, -6 and -7, resulting in apoptosis [14].

The apoptotic pathway is also regulated by the B-cell lymphoma 2 family (Bcl-2) proteins which control apoptosis by governing MOMP, and it consists of pro-apoptotic members (such as Bak, Bax, Bad, BID, Bcl-Xs, Bik, Bim, HRK, PUMA and Noxa) and anti-apoptotic members (such as Bcl-Xl, Bcl-W, Bcl-2, Bfl-1 and MCL-1), pro-apoptotic proteins, translocated to the mitochondria and causes apoptosis, and reduction of antiapoptotic proteins also induces apoptosis.Sometimes Bcl-2 binds toBeclin-1 protein and inhibit apoptosis and also autophagy, but if C-Jun N-terminal protein kinase 1 (JNK1) -which belongs to protein kinase family, and are responsive to stress stimuli- is triggered by cell stress, it phosphorylates the regulatory loop of Bcl-2 and thus break up the interaction between Bcl-2 and Beclin-1 and activation of caspase-3 mediated apoptosis [14].

Apoptosis is also induced by suppression of tolemerase (which are transient DNA sequences that preserve chromosomal integrity during mitosis) and it consists of human telomerase RNA (hTR) and other proteins like human telomerase reverse transcriptase (hTERT) which is found in most of cancer cells. hTERT employs human telomerase RNA (hTR) as a pattern to constantly synthesize telomeric DNA sequences at chromosome termini, so continuing cell mitosis and replication, thus, the suppression of telomerase activity in cancer cells interferes with telomeric repair, resulting in a progressive decrease of telomere length with each replication cycle, reduce cell replication, thereby preventing cell proliferation and cause apoptosis [15].

NF-kappaB is essential in inhibiting apoptosis via multiple pathways. First pathway is increasing of antiapoptotic protein expression. The NF-kappaB-responsive anti-apoptotic genes contain Bcl-XL, cIAP1, cIAP2, XIAP, A20, TRAF-2, and c-FLIP, which enhance cellular survival by making cells less susceptible to apoptosis stimulated by various stimuli. Second, NF-kappaB also exerts a negative regulatory effect on the activation of the apoptotic JNK pathway. Third, NF-kappaB inhibits apoptosis by opposing p53, potentially via fighting for transcriptional co-activators. Ultimately, NF-kappaB diminishes the expression of phosphatase and tensin homolog (PTEN) to stimulate Akt, hence enhancing cell endurance and proliferation. So inhibiting this pathway can cause apoptosis [16].

The Wingless-related integration site (Wnt) pathway is a crucial regulator of the apoptosis process. It regulates cell proliferation, migration, differentiation of almost every body tissue and regulates developing embryo process. Wntsignaling mutated expression is frequently associated with several diseases including lung cancer. Apoptosis can take place at several signaling pathways in cancer. Several reports discussed these pathways in detail [14][12].Figure A shows the discussed mechanisms in treating cancer.Other mechanism for treating lung cancer is cell cycle regulation/arrest through Tumor suppressor genes. For normal cell to go through mitosis and divide into two cells, it enters a gap phase called (G1 phase), where cells increase in size and produce organelles, before DNA replicates in synthesis Phase (S) and then enter another gap phase called (G2), where they prepare themselves for division. Sometimes there is a resting phase named G0 in which the cell stops division. Subsequently, the cell enters multistep mitosis phase (M phase) and produce daughter cells. According to the previous information, cell cycle arrest could be at any phase of cell cycle so cells could not complete the normal cell cycle leading to inhibiting cell growth. P53 and phosphatase and tensin homolog (PTEN) are tumor suppressor genes that have a major role in maintaining cell cycle. P53 is a transcription factor which promotes DNA repair and growth arrest so eventually inhibit proliferation of cancer cells. Also, PTEN gene has a role in cell arrest at G1 phase and so limits the proliferation of cancer cells [17].

Tyrosine kinase inhibitors (TKI) are a way for managing lung cancer. It is a type of cancer targeted therapies which interferes with specific molecular targets responsible for tumor growth or progression, so it also reduces the nonselective chemotherapy side effects on body cells and concentrates on the targeted cells. Tyrosine kinases can be classified as receptor protein kinases and non-receptor protein kinases. Certain (TKIs) shown their anticancer efficacy by targeting the epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptors (VEGFR), and platelet-derived growth factor receptors (PDGFR).) which are associated with the regulation of several neoplastic processes including tumor cell motility, invasion, metastasis,cell cycle progression and apoptosis suppression [18].

epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) are commonly used mechanism in targeting lung cancer as EGFR Performs a vital role in governing normal cell proliferation, apoptosis, and many biological processes and is a element of the receptor tyrosine kinase (RTK) family, which plays a huge role in cancer formation, so using inhibitors can aid in stopping cancer cell development. vascular endothelial growth factor receptors (VEGFR) tyrosine kinase inhibitors (TKI) are used as mechanism in targeting lung cancer cells. Endothelial cells are the primary cells immediately engaged in angiogenesis. (VEGF) can stimulate angiogenesis via various pathways. Angiogenesis is developing new blood vessels from the existing vasculature, and is an important hallmark in the formation of malignant tumors [19]. (VEGF) is released during tumor formation, it is particularly specific to vascular endothelium and modulates both vascular proliferation and permeability which are crucial to develop new cancer cells. Elevated VEGF levels are correlated with heightened microvascular density, cancer recurrence, and worse survival rates.So inhibiting (VEGFR) can aid in stopping cancer cell development [18].

PI3K/AKT/mTOR inhibitor pathway which is called Phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway has an essential function in proliferation, cellular survival and angiogenesis and is often dysregulated in human malignancies [20]. Receptor tyrosine kinase (RTK) can activate lipid kinase, phosphatidylinositol 3-kinase (PI3K), and the serine/threonine kinase, Akt (p13k/AKT) pathway which targets proteins downstream, facilitating proliferation, carcinogenesis, invasion, and metastasis of cancer cells, so targeting this pathway may affect cancer cell progression. Another way to influence (AKT) is using mTOR which is an element of the phosphatidylinositol kinase related kinase family that effects (AKT) role as a molecular sensor regulating protein synthesis, so application of mTOR inhibitor can help in cancer treatment in addition to p13k and AKT inhibitors [21][22][23]. Autophagy (Self-eating) which is self-destructive pathway in which forming autophagosomes is causing cell death. Several reports studied the function of autophagy in cancer treatment [14][12].

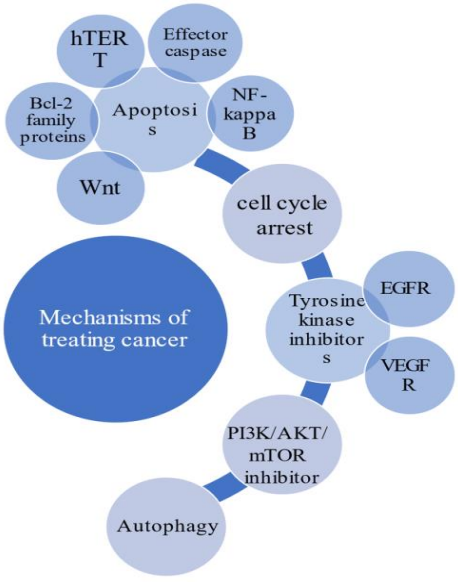

Figure A: Mechanisms of treating cancer.

Natural plants have been used as a traditional medicine for decades for treating different diseases. Recently, natural plants and its constituents have been extensively utilized as adjunctive therapy with chemotherapy to increase chemotherapy effect on cancer cells or to decrease chemotherapy resistance or to reduce its side effects. Ongoing chemotherapy and additional treatments, come with a long list of adverse effects. Many phytochemicals are safe for other cells and may have anticancer activity for cancer cells. Making use of these advantageous qualities could contribute to the improvement of the method of treating cancer with less side effects [24]. Natural product compounds exhibiting anticancer properties possess molecular pathways that facilitate the progress of anti-malignancy medicines, such as triggering apoptosis, reducing angiogenesis and metastasis, reversing multidrug resistance, and targeting reactive oxygen species signaling [25]. The potential of medicinal plant extracts and their constituents for treating lung cancer looks promising, especially when used in conjunction with standard anti-cancer medications [26]. Natural products prevent organ damage brought on by cisplatin by regulating a number of gene transcription factors causing necrosis or apoptosis in cells [11]. It has been proven that the studied extracts and essential oils of natural plants affect lung cancer through a diversity of pathways, such as decreased tumor weight and volume, cell viability, and cytokine regulation. Apoptotic protein expression, the ratio of cell cycle arrest in the G2/M phase and G0/G1 phase and cytochrome c levels (which generate apoptosome which activate caspase-3, -6 and -7thus induce apoptosis) were all elevated by certain plant ingredients. Furthermore, in lung cancer cells, natural products (NP) stimulate apoptotic pathways such as p-JNK, Akt/mTOR, PI3/AKT and Bax pro-apoptotic protein [26]. Vincristin,Vinblastine, Resveratrol,Fisetin, Celastrol and Topotecan are phytochemicals present in natural plants used in lung cancer treatment according to [24]. Linalool which presents in *Ocimumbasilicum* can increase cell cycle arrest during G0/G1 phase, inhibit cell migration, proliferation and can have anti-metastatic activity on A549 lung cancerous cell lines [27].

Also, Carvacrol isolated from *Origanum vulgare* and *Thymus vulgaris* when administered to H460 and A549 cell lines reduces AXL expression and phosphorylation in cancer cells, decreases viability and migration in cells [28]. Furthermore, Thymoquinone down-regulated Bcl2 proteins, and Up-regulated Bax, and Bax/Bcl2 ratio when administered to A549 cell lines [29]. Some plants that have proved their efficacy as anticancer agents will be discussed in this article.

Allium sativum L.

A. sativum, commonly known as garlic, is a bulbous perennial plant belongs to family Alliaceae and characterized by a potent onion-like aroma and a pungent taste, utilized as a flavoring ingredient, food additives, and for medicinal purposes for over 5,000 years. Garlic is also recognized as stinking rose, Allium, Rocambole, rustic treacle, ajo, nectar of gods, treacle of poor man, clove garlic and poor's camphor. *A. sativum* ingredients are categorized into two classes based on solubility, allyl sulfur lipid-soluble compounds, including diallyl trisulfide (DATS) and diallyl disulfide (DADS, while the other consists of water-soluble compounds, including the γ-glutamyl S- allylcysteine (SAC) group, which includes SAC and S-allylmercaptocysteine (SAMC). According to Garlic content, it can decree blood glucose, total cholesterol, LDL cholesterol and cardiovascular diseases. It is also used as antimicrobial, antiviral, antifungal, anti-protozoal and antitumor. Regarding garlic anticancer activity, it has the cabapility to decrease carcinogen binding to DNA, promote carcinogen degradation, act as an antioxidant and free radical scavenger, and control cell proliferation, apoptosis, and immunological responses [30] [31]. It is found that administering raw garlic to healthy people decreases the lung cancer threat so *A. sativum* could be utilized as chemo preventive agent [32]. Also, allicin which is present in garlic induces autophagy and apoptosis pathways in A549 cell-lines via ROS buildup and promotes S/G2-M phase arrest under both normal and low oxygen conditions [33].

Artemisia vulgaris L.

A. vulgaris is Known as Mugwort, belongs to family Asteraceae which consists of further than 500 species. It grows naturally across Asia, Europe and North America. It is traditionally utilized as anthelminthic, antiseptic, antibacterial, antispasmodic, carminative, digestive, treating hepatic disorders, diaphoretic, expectorant, in managing stress, insomnia, irritability, depression and many other traditional uses [34]. It has long been established that the genus Artemisia contains artemisinin, a significant bioactive substance and is medically used as antimalarial and has shown anticancer activity. Other Artemisia compounds that influence several signalingcascades have as well been considered promising cancer treatments through their apoptosis induction, cell cycle obstruction and decreased proliferation rate [35]. Methanolic extract of *A. vulgaris* had cytotoxic activity counter to NSCLC (A549), cervical cancer cell (HeLa) and estrogen-dependent breast cancerous cell line (MCF7) [36]. Vulgaris in ethanol has pro-apoptotic and antiproliferative actions counter to A549 cells [4], other than its hepatoprotective effect against cisplatin treatment when administered to mice as it decreases ALT, AST, ALP and TSB liver enzyme levels [37].

Boswelliacarterii L.

Frankincense resin is derived from Boswellia genus trees, belonging to family Burseraceae. Incisions are performed on the tree trunks to yield extruded gum, which manifests as a milky resin. The resin solidifies into a gum resin with an orange-brown color called frankincense [38]. Gum resin Frankincense has historically been applied to treat number of illnesses that

have inflammatory symptoms, and it also has low side effects while reducing the symptoms of many different diseases [39]. *B. carterii*, which is found in East Africa and China,or its components induces neutrophils apoptotic mechanism by activation of PKC and PI3-K dependent pathways thus may has anti-inflammatory activity [40]. Furthermore, its anti-inflammatory activity, *B. carterii* aqueous extract and its silver nanoparticles exhibited antimicrobial and antibacterial activity [41]. Immunomodulatory properties of *B. carterii* extract had been proved [42]. The *B. carterii*oleogum resin has demonstrated substantial chemo preventive effects in recognized carcinogenesis animal models [43]. Frankincense also showed potent antitumor effects across various cancer types as its oil inhibits cell survival rate and promotes apoptosis in cultivated J82 bladder cancer cells [38] and its content of 3-O-acetyl-11-keto-ß-boswellic acid increases the cell cycle G2/M phase inhibition in glioblastoma thus, shows anti-tumor actions. Acetyl-11-keto-β-boswellic acid (AKBA) present in *B. carterii* increases sensitivity of cisplatin by cell cycle arrest thus induces apoptosis in NSCLC [39].

Camellia sinensis L.

C. sinensis belongs to family Theaceae and is cultivated in a minimum of 30 nations globally. The green tea beverage is an infusion of the dried leaves of *C. sinensis* and is widely used medicinally due its active component catechines[44]. It is commonly recognized that green tea has anti-inflammatory and anti-cancer effects. Polyphenols, particularly green tea's primary catechin, Epigallocatechin-3-gallate (EGCG), are promising in preventing stomach, pancreas, prostate, lung and breast pulmonary and mammary cancers [45]. Green tea exhibits significant antioxidant properties, and its polyphenols (GTPs) are involved in the protection against DNA damage produced by carcinogen, facilitating death of eoplastic cells and inhibiting angiogenesis [46]. Also, EGCG inhibit PI3K/mTOR.in HCC827-Gef cells human pulmonary carcinoma cells showing anticancer effect [47]. EGCG and other components as theaflavingallate, theaflavindigallate and epicatechingallate had strong affinity to EGFR so may have potential applications in NSCC treatment [48].

Cinnamon zeylanicum L.

C. zeylanicum or *Cinnamomum verum* which is also called as “true cinnamon” belongs to family Lauraceae. Numerous bioactive substances, including eugenol, cinnamic acid, linalool, *β*-caryophyllene, coumarin, trans cinnamyl acetate, and 1,8 cineole, are found in cinnamon extract or its essential oil. These substances have a number of biological effects, such as anti-inflammatory, anti-diabetic, anti-arrhythmia, anti-cholinesterase, anti-lipid oxidation and anticancer properties. For the antineoplastic activity; cinnamon containing Eugenol and cinnamaldehyde can suppress pulmonary (NCI-H322) and breast (T47D) carcinoma cell lines growth [49]. Cinnamic acid could suppress NF-kB, AP-1 and STAT3 and also decrease the signaling of MAPK and PI3K/Akt in A549 pulmonary carcinoma cells [50]. Also, cinnamon aqueous extract has demonstrated the ability toinhibit the proliferation of 5637 bladder carcinoma cells by blocking glycolysis and inducing apoptosis, while the n-hexane, chloroform, and ethyl acetate fractions suppressed the viability of three pulmonary carcinoma cell lines A549, H-1650 and H- 1975 [51].

Curcuma longa L.

C. longa is a Rhizome-bearing plant belongs to family Zingiberaceae, indigenous to South and Southeast Asia, including China, Indonesia, Malaysia, Nepal, Jamaica, El Salvador, Haiti, Taiwan, India, Pakistan and Bangladesh. It is utilized as a food spice and a natural coloring agent thanks to its significant color and has high medicinal uses as antifungal, antiviral, antiparasitic, antibacterial, analgesic, digestive-protecting anti-inflammatory, antioxidant, antidiabetic activities. The plant can treat Alzheimer’s disease, arthritis, cardiovascular disease, hepatic and renal problems along with handling various cancer types. The yellowish color of the spice is mostly attributable to the curcumin present in Turmeric, which is attributed to many of its purported therapeutic properties [52]. Curcumin exhibits the capability to serve as a valuble adjunct in the manadement of solid organ tumors by modulating oncogenes such as p53, bcl-XL, c-myc and egr-1, enzymes like lipoxygenase (LOX) and cyclooxygenase (COX) , transcription Factors such as NF-kB, STAT-3, and AP-1 and protein kinases include mitogen-activated protein kinases signaling enzymes (MAPK) [53]. Curcumin demonstrated suppression of extracellular signal-regulated kinase (ERK) 1/2, EGFR, and COX-2 in pulmonary adenocarcinoma cells, resulting in an increased rate of cancer cells death and decreased survival of lung carcinoma cells [52].

Glycyrrhiza glabra L.

G. glabra is among 20 known and accepted species within Glycyrrhiza genus pertaining to the Fabaceae family [54]. *G. glabra* has traditionally utilized thousands of years ago to treat several diseases as it is utilized as antiulcer, antiviral, antibacterial, anti-inflammatory, antispasmodic, antacid, antihistaminic, antiallergic, diaphoretic, diuretic, hypotensive, laxative, expectorant, sedative, emollient, analgesic, wound-healing, tonic, potency enhancer, detoxicant, capillary-strengthening and antioxidant [55]. Liquorice extract and flavonoids belonging to it also can function as hepatoprotective, antibacterial and anticancer as liquorice flavonoids suppress cell cycle at different phases causing apoptosis, thereby playing a rule in inhibiting cancerous cell proliferation [56]. Some *G. glabra* components as saponins, flavonoids and phenolic

compounds contribute to its activity such as glycyrrhizinic acid which can promote antimetastatic qualities in gastric cancer, resulting in apoptosis and tumor suppression via modulating various signaling pathways linked to cellular growth and development [54]. Also, a Combination of isoliquiritin, liquiritin and isoliquiritigenin in liquorice results in apoptosis of A549 lung cancerous cells through multiple signal pathways [57].

Nigella sativa L.

N. sativa which is recognized as Black seed belongs to family Ranunculaceae and is indigenous to North Africa, Southwestern Asia and Southern Europe and is cultivated in various regions as Middle Eastern Mediterranean region, Turkey, Syria, Saudi Arabia, Pakistan and India. It has already been traditionally employed widely as a result toits medical advantages as it can treat asthma, bronchitis, rheumatism, diarrhea, skin disorders and diabetes. *N. sativa* is also used as analgesic, antihypertensive, diuretic, anthelmintic, spasmolytic, hepatoprotective, renoprotective, gastro protective, appetite stimulant, increase milk production in nursing mother, antimicrobial, anti-inflammatory, immunomodulatory, antioxidant and also anticancer agent. *N. sativa* contains thymoquinone which is an exceedinglypotent chemical constituent of black seed and is accountable for most of its pharmacological effects. It also contains carvacrol, *P*-cymene, thymol, dithymoquinone, nigellicimine, nigellicine, nigellidine and other various components. As an anticancer agent, thymoquinone present in *N. sativa* reduced human osteosarcoma cells SaOS-2 and induced cell apoptosis [58].Also apigenin was recognized as the lead compound against ALK receptor protein, whereas Salfredin B11 was designated as the lead compound against EML4 receptor protein participating in lung cancerous cells pathogenesiswhen using docking to test *N. sativa* lung anticancer activity [59].

Ocimumbasilicum L.

O. basilicum, named sweet basil belongs to family lamiaceae. and has exhibited antimicrobial, antifungal, anti-inflammatory, insecticidal, antiparasitic, antioxidant, anticancer, cardioprotective, immunomodulatory, hepatoprotective, anti-osteoporotic, neuroprotective activities together with additional advantageous health effects [60]. Basil's anti-cancer, anti-microbial, anti-inflammatory, and radioprotective properties are its most significant pharmaceutical uses. It contains flavonoids, phenolic acids, polyphenols, and phenolics [61]. Carvacrol, a monoterpenoid phenol present in the essential oil of the Lamiaceae family, was proved to enhance the expression of Bax, Bcl2, p-JNK, Cyt C, Cas-3, Cas-9 and β-actin in lung tissue and reduces lung tumor growth and tumor weight by 34.2% and 62.1%, respectively [26].

Panax ginseng L.

P. ginseng rhizome or root belongs to family Araliaceae and originates from Korea, China, and Russia has served as a significant herbal treatment in traditional Chinese medicine for centuries It has primarily been utilized as a treatment for weakness and fatigue. It has been proved in various studies that *P. ginseng* has enhanced attention, processing capabilities, auditory response time, social performance, mental well-being, accelerated simple reactions and abstract cognition. Also, it boosts the immune system, erectile function, sexual desire, intercourse satisfaction, improve the overall performance of cardiovascular and nervous systems and exhibits anticancer effects [62]. The most powerful constituents in *P. ginseng* are ginsenosides, triterpene saponins responsible for most of its psychological and physical actions as Ginsenosides restrict the NF-κB-mediated stimulation of cancer metastasis and immunological resistance and Rk1 ginosenosides and Rg5 ginsenosides diminished the incursion of the A549 human lung cell line [63].

Rosmarinus officinalis L.

Rosemary belongs to Lamiaceae familyand is present in the area of Mediterranean and Asia and nowadays is cultivated in many regions as its beautiful shape and aroma It is utilized in culinary applications, and its oil may be applied to shampoos, soaps, and cosmetics. Over the years *R. officinalis* had been utilized traditionally as antispasmodic, carminative, digestant, antihypertensive, diuretic, antidiabetic, antiepileptic, diaphoretic, to treat cough, cold, headache, tiredness, rheumatism, muscular and joint pains,menstrual disorder it also enhances memory, reduces insomnia, minimizes mental tiredness, reduces nervous anxiety and tension, handles nervous depression and other nervous disorders [64][65]. Rosemary and its components, such as carnosic acid besides rosmarinic acid and carnosol have antitumor properties which attributed to various mechanisms, including its antiangiogenic, antioxidant characteristics, epigenetic influences, modulation of the immune response, anti-inflammatory actions, alteration of specific metabolic pathways, and enhanced genes expression involved in tumor suppression. [66] [67]. *R. officinalis* has Antiproliferative activity targeting colon, breast, skin, prostate, leukemia and pulmonary cancer cells causing apoptosis by different mechanisms [68].

Salvia officinalis L.

S. officinalis commonly called sage, belongs to family Lamiaceae is common in the Middle East, Mediterranean areas and in south Sinai in Egypt. Itis widely used in cosmetics, cooking and folk medicine as it has traditionally been employed in the

management of several diseases including ulcers, gout, seizure, inflammation, rheumatism, dizziness, hyperglycemia, paralysis, diarrhea and contributesin treating depression, memory disorders and Alzheimer's disease. It is employed in the management of disorders affecting the upper respiratory tract.like asthma [69] [70] [71]. Its anticancer activity was where extracts of S. officinalis showed pro-apoptotic and growth-suppressingeffects on cell lines derived from lung carcinoma (A549), colorectal cancer (HCT-116, HCT15, CO115, HT29), breast cancer (MCF-7), insulinoma (RINm5F), cervix adeno carcinoma (HeLa), laryngeal carcinoma (Hep-2), melanoma (A375, M14, A2058, B16), and oral cavity squamous cell carcinoma [70] [71]. *S. officinalis* components contribute to its anticancer activity are luteolin, cirsiliol and carnosol found in methanol-based extract of *S. officinalis* suppressed the growth of A549 and HepG2 cancerous cells [72].

Thymus vulgaris L.

T. vulgaris L. belongs to mint family (lamiaceae). It has great aroma and is utilized as flavoring agent and in cooking. It is common in the Mediterraneanandneighboring countries, Northern Africa, and some parts of Asia. *T. vulgaris* has been grown in Egypt, Algeria, Morocco, Libya, Tunisia, Cameroon, South Africa and Nigeria. It is utilized as carminative, disinfectant, anthelmintic, astringent, antimicrobial, antiseptic and as gargles. It is helpful in treatment of laryngitis and inflammation. It could also act as antifungal, antiviral, antibacterial, anti-inflammatory and antioxidant [73] [74]. *T. vulgaris* was found to possess anticancer properties. activity in many researches.

Thymol treatment decreases the viability of non-small cell lung cancerous cells (A549), while it does not exhibit cytotoxic effects on human PBMCs (Peripheral blood mononuclear cells) [75]. In another study, [76] found that essential oil obtained from *T. vulgaris*. [76] have found that the essential oil of T. vulgaris exhibits antiproliferative effect against certain cancerous cell lines as H460 (non-small-cell lung cancer cells), MCF-7 breast cancer and MOLT-4 (human lymphoid cell lines) and demonstrated the cytotoxic efficacy of thyme essential oil against lung cancer and acute lymphoblastic leukemia cell lines attributable to its thymol and *p*-cymene constituents.

Trigonellafoenum-graecum L.

Fenugreek is classified underthe Fabaceae family, utilized as a supplement to diet and offers benefits in the management of diabetes, atherosclerosis and in liver, renal and cardio protection. Fenugreek and its bioactive ingredient contribute in tumor inhibition by modifying the function of several genes, such as those that induce apoptosis, reduce tumor suppressor genes, and inhibit tumor necrosis factor. Fenugreek seeds include, sapogenin, galactomannan trigonelline, and 4-hydroxyisoleucine compounds, which provide anti-diabetic breast anticancer treatment, also include diosgenin which down regulated activation of ER and induce the expression levels of p53 protein in MCF-7 breast carcinoma cells.

The methanolic extract treatment of fenugreek had a cytotoxic impact and promoted apoptosis in HepG2 liver cancer cells by the overexpression of Bax, p53, PCNA and the stimulation of caspase-3 [77]. Research has revealedthat application of indirubin-3-monoxime with thymoquinone (TQ) (phytochemical compound found in many plants as *N. sativa* or *Trigonellafoenum-graecum* on A549 cancerous cells increased apoptosis markers and reduced the Bcl-2/Bax ratio, resulting in inhibiting migration and the spread of metastasis in the cancerous cells [26]. Also, Diosgenin and its synthetic analogue P2, DiP and P2P (P2Ps) elicit cell cycle arresting in the G0/G1 phase and death in A549 and PC9 human NSCLC cells [78].

Zingiber officinale L.

The rhizome of *Zingiber officinale* is classified under the Zingiberaceae family known as ginger. It is among the oldest therapeutic plants. traditionally utilized in Indian, South-East Asian, Chinese, Arabian and African cultures thanks to its biological activity. It is utilized as a spice, flavoring agent and in herbal remedy attributable to its huge immunostimulant, antioxidant, antimicrobial, anti-inflammatory, antidiabetic, hepatoprotective, anti-platelet aggregation, anti-atherosclerotic, anti-obesity, antiemetic, antipyretic, gastroprotective, cardiovascular protective,neuroprotective, anthelmintic, antipyretic, antifungal,alangesic and last but not least anticancer activity [79][80]. *Z. officinale* components of sesquiterpens together with phenolic compounds may be responsible for its biological activity.6-gingerol and 6-shuagols, the key components in *Z. officinale* extract caused G2/M transition cell cycle arresting thus, cause apoptosis in prostate carcinoma cells (PC3 cells)) [81]. Also 6-gingerol, sitosterol and other 4 Compounds present in ginger extract could prevent against colon cancer by regulating EGFR tyrosine kinase inhibitor resistance and PI3K-Akt signaling pathway [82].

On the other hand, 6-paradol and 6-shogaol are the compounds responsible for the anticancer effect of ginger. as they suppress hTERT expression and telomerase function in A549 cancerous cells [83]. Natural plants, its active constituents, and anti-cancer mechanisms are presented in table 1. Structures of some of the isolated compounds having anticancer activity are represented in figures from 1 to 4.

Table (1): Natural plants, its constituents and mechanisms in treating cancer.

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Allium sativum L.			
Lung cancer			
Cycloalliin (1)	A549	Decreases transforming growth factor (TGF)-ß-induced EMT and invasive capability of lung carcinoma cells.	[84]
Diallylsulfide (2) and diallyldisulfide	NCI-H460	Diallylsulfide (2) and diallyldisulfide _NCI-H460 _Diallyldisulfide increases p53 in H460 cells while diallylsulfide increases Bax levels and decreases Bcl-2 levels in H460 cells.	[88]
Ethanolic extract nanoparticles	A549	Induces cytotoxicity through the generation of reactive oxygen species resulting in cellular damage and eventually cell death.	[86]
Garlic small extracellular vesicles(SEVs)	A549 lung cancer cells and A498 Human kidney carcinoma cell line.	Diminishes the anti-apoptotic Bcl-2 protein levels with elevation in pro-apoptotic Cas3 gene expression levels and diminishes the expression levels of the angiogenic protein VEGF following SEVs application in cancerous cells.	[87]
Z-Ajoene	A549 and H1299	Decreases cancer cells proliferation and translocation and increase expressions of pro-apoptotic Bax, cleaved caspase 3, and cleaved caspase 9 in cells treated with Z ajoene but exhibiting a low expression of Bcl-2 anti-apoptotic protein in a way dependent on dosage causing apoptosis.	[85]
Other cancer types			
Diallyl trisulfide	PCa prostate cancerous cell lines	Reduces the growth of cancerous cell lines by causing apoptosis through the downregulation of Bcl-2 protein and the induction of the extracellular signal-regulated kinase 1/2 (ERK) and c-Jun N-terminal kinase (JNK) pathways.	[30]
	Human melanoma A375 cells	Increases the intracellular reactive oxygen species levels, DNA damage, induction of endoplasmic reticulum stress, and mitochondria-mediated apoptosis.	[31]
Artemisia vulgaris L.			
Lung cancer			
Artemisinin (3)	A549	Reduces A549 cell survival.	[89]
Artesunate (4)	A549	Increases G2/M phase cell cycle arresting and augments radiosensitivity of A549 cells.	
Ethanolic extract of the leaves	A549 lung cancerous cell lines	Inhibitsthe Wingless-related integration site (Wnt) signaling Pathway and the viability of cancerous cell line viability.	[4]

Extract/isolated compound	**Cell line**	**Mechanism/ Action**	**Reference**
Naringin (5)	A549	Enhance beta-carotene effect on DNA damage caused by a potent tobacco related carcinogen in humans.	[90]
Other cancer types			
Aqueous extract	Colon cancer (RKO) cells, human breast carcinoma (T47D) cells and prostate cancer (PC-3) cells	Elevation of caspase-3 thus induce apoptosis.	[95]
Essential oil	HL-60 cells	Induces apoptosis by activating the caspase cascade (caspases-3, -9, and -8)	[93]
Essential oil of nano-emulsion	MCF-7 breast carcinoma cells.	Decreases VEGF gene expression thus decrease angiogenesis and reduce cells at G1, S, G2-M phase.	[91]
Eupafolin (6)	JB6 Cl41 and KYSE450 cells esophageal cancer cells	Inhibits T-LAK cell-originated protein kinase(TOPK) activities which is present in several cancer cells.	[92]
Methanolic extract	MDA-MB-231, MDA-MB-468, MDA-MB-453 and MCF-7 breast cancerous cells.	Induces cytotoxicity with TRIAL (Tumor necrosis factor-related apoptosis-inducing ligand) and reduces phosphorylation of P65.	[94]
Bosweliacarterii L.			
Lung cancer			
AKBA (7)	(NSCLC)	Arrests the cycle of the cell at the G0/G1 phase thus, induces apoptosis.	[99]
	A549 and NSCLC CELLS (H460 and H1299)	Increases cisplatin sensitivity to NSCLC cells by triggering apoptosis through cell cycle G0/G1 phase arrest, suppressing autophagy through targeting the p21-dependent signaling pathway.	[100]
α- and β-boswellic acid (8).	60 NCI Cell Lines,lung cancerous cells are among them.	Showed cytotoxicity on cancer cells.	[102]
11-carbonyl-b-boswellic acid	NSCLC (H446) lung cell	Induces apoptosis by cell cycle G2-M phase arrest, Up-regulates signaling pathway of JNK and down-regulates surviving proteins.	[101]

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Essential oil	A549 lung cancerous cells	Inhibits cellular proliferation and viability of cancer cells.	[96]
	A549 cell lines.	Increases apoptosis with its PG-nano emulsion by inducing pro-apoptotic genes(Bax, Caspase 8, p53, DR5, FAAD) and reducing anti-apoptotic genes (Bcl-2, STAT-3 and NF-kB) thus inhibits reoccurrence.	[97]
	A549 cell lines, MCF-7 and HS-1 cell lines	Induces apoptosis	[98]
Other cancer types			
Essential oil	Breast cancer cells	Regulates AMPK/mTOR pathway thus induces apoptosis	[103]
	Liver cancer cells SMMC-7721	Increases expression ratio of bax/bcl-2.	
Camellia sinensis L.			
Lung cancer			
Aqueous extract with *Ocimumgratissimum L.* extract	A549 cells and male Swiss albino mice.	Increases antioxidant action, antioncogenic potential and chemo preventive action against the generation of lung tumors.	[104]
Epigallocatechin-3-gallate EGCG (9)	HCC827-Gef cells human pulmonary carcinoma cells.	Inhibits p13K/mTOR pathway.	[47]
	A549 cells and H1299 cells	Decreases proliferation by suppressing NF-kBsignaling pathway.	[107]
	Human NSCLC cells A549, H1299 and Lu99	Suppresses the proliferation of lung cancerous cells by restoring T cell activity by inhibiting PD-L1/PD-1signaling.	[108]

Extract/isolated compound	**Cell line**	**Mechanism/ Action**	**Reference**
	A549 and normal FR-2 cells	Increases cell cycle G2/M phase arrest, modules Bax/blc-2 ratio thus, promotes apoptosis and suppresses migration of A549 cells.	[109]
	A549 cells.	Induces apoptosis by Triggering of caspase-3 and caspase-9 and inhibits hepatoma-derived growth factor (HDGF) in lung cancerous cell lines thus, increase sensitivity to cisplatin therapy.	[110]
(-)-Epicatechin (EC) (10)	Hel-299 A549 lung carcinoma cell lines	Inhibits cellular proliferation and induces apoptosis, protects normal cells, reduces side effects and increases the cytotoxic efficiency of cisplatin on malignant cells.	[111]
Glucosylated EGCG	NCI-H292, NCI-H441, NCI-H1781, NCI-H1975, and A549 cells.	Decreases phosphorylation of EGFR in NCI-H1781 cells and decreases cellular viability in NSCLC. Shows more decreasing in proliferation when combined with cisplatin/paclitaxel.	[106]
Nano-emulsion of EGCG	H1299 and A549 cells.	Stop the growth, colonization, invasion, and the migration of lung cancerous cells via activating AMPK signaling pathways.	[105]
Polyphenols	NSCLC-NCI-H460	Inhibites the cancerous cells proliferation and promotes apoptosis by elevating P53 protein expression and by suppressing Bcl-2.	[112]
Other cancer types			
Polysaccharides	Human pancreatic cell lines (PC-3, LNCaP, C4-2B and DU145)	Induces apoptosis by increasing caspae-3 protein expression, bax/bcl-2 ratio, and decreasing miR-93.	[113]
Cinnamon zeylanicum L.			

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Lung cancer			
chloroform, n-hexane and ethyl acetate fractions	Human A549 lung cell lines, H-1650, H-1975, primary non-cancerous cell line HUVEC and zebrafish embryos.	Inhibits cellular viability in human lung cancerous cells and induces neurotoxicity in zebrafish embryos.	[51]
Cinnamaldehyde (11)	A549 cell lines.	Cinnamaldehyde with hyperthermia combination suppresses the survival factors, increases the apoptosis markers, increases cell life cycle arrestduring the G2/M phase and increases the generation of mitogen-activated protein kinases (MAPK) phosphorylation and reactive oxygen species (ROS).	[115]
Copper nanoparticles of aqueous extract.	NCI-H2126, NCI-H1437, NCIH1573, and NCI-H661 lung cell lines	Increases cytotoxicity to cancerous cells and antioxidant potential.	[114]
Cuminaldehyde	Human pulmonary squamous cell carcinoma NCI-H520 cells.	Induces apoptosis and reduces proliferation by increasing pro-apoptotic bak and bax genes and reducing the anti-apoptotic bcl-2 and bcl-XL genes, stimulation of caspase-3 and -9, releasing of cytochrome c and morphological characteristics of apoptosis, also decreasing of topoisomerase I and II functions and increasing of lysosomal vacuolation with increased VAC and cyto- toxicity.	[116]
Other cancer types			
Essential oil	Sprague–Dawley female rats, BALB/c female mice, MCF-7 and MDA-MB-231cell line breast carcinoma models	In vivo: Increases Bax and caspase-3 expression Also decreases VEGF, Bcl-2, CD24 and Ki67 expressions and MDA levels. In vitro: Increases the cells population in sub-G0/G1 and reduces the G1 cells only also deactivates the Bcl-2 protein.	[118]
Ethanolic extract	Breast cancer MDA-MB-231 cell line	Induces apoptosis and cytotoxicity to cancer cells but did not show cytotoxicity to normal cells.	[119]
Methanolic extract and Cinnamaldehyde	SCC-4, SCC-9, and SCC-25 oral cancerous	Induces cell life cycle arrest, autophagy and apoptosis, activity and decreases expression of several PI3K-AKT-mTOR pathways linked to VEGF, COX-2, Bcl-2, NF-κB, and proteins following therapy.	[117]

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
	cell lines		
Water extract	MCF-7 cell lines.	Inhibits cellular viability and has cytotoxic activity to breast cancerous cells during two distinctincubation periods.	[120]
Curcuma longa L.			
Lung cancer			
Curcumin (12)	A549	Downregulates the NF-κB and reduces JAK2 activity by targeting the JAK2/STAT3 pathway.	[52]
	A549 cells in mice	Reduces tumor size and weight, downregulates Notch and HIF-1 mRNA expression, and inhibits VEGF and NF-κB expression.	[122]
	NCI-H1299, NCI-H460, NCI-H520 and NCI-H446	Curcumin with combination of Paris Saponin II Induce the JNK and p38 phosphorylation while inhibiting PI3K in NCI-H446 and NCI-H460 cells, augment JNK phosphorylation in NCI-H1299 cells, and elevate ERK and P38 phosphorylation while suppressing PI3K in NCI-H520 cells.	[123]
	A549	Reduces cancer cells proliferation by Wnt/β-catenin pathway.	[124]
	A549	Induces apoptosis by cell life cycle arrest at growth/mitotic phase (G2/M) and has synergistic effect with apigenin.	[53]
	PC-9 NSCLC	Enhances the growth inhibition and DNA damage (GADD) 45 and 153 in a p53-independent fashion, while also suppressing pulmonary cancerous cells proliferation in addition to promoting cell cycle arresting at G (1)/S phase accompanied by pronounced activation of apoptosis.	
	A549 and H460	Decreases the expansion of human lung cell lines through G0/G1 cell life cycle arrest.	
	A459 and MCF7	Curcumin with aleovera and polycaprolactone (PCL) nanofibers reduce viability of cancerous cells more than curcumin/PCL alone or Curcumin/Neem/PCL.	[125]
Curcumin and its derivative (CU17)	A549	Increase p53-independent apoptosis in A549, induce cell cycle G2/M arrest and Bax expression but decrease the level of p53, p21, Bcl-2, and pERK1/2 expression.	[121]
Other cancer types			
Curcumin	SGC-7901 gastric cancer cells	Causes apoptosis by altering the mitochondrial membrane potential (MMP) and increases the Cytochrome c leakage into the cytoplasm.	[52]
	B cell chronic lymphocytic leukemia (CLL-B)	Enhances apoptosis through the restriction of STAT3 and AKT, NF-κB and X-linked inhibitor of apoptosis protein (XIAP).	
Glycyrrhiza glabra L.			

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Lung cancer			
Glycyrrhizin (13)	PDX mice and NSCLC cell line (HCC827)	On mice: Suppresses the expansion of lungtumor. On HCC827 cell lines downregulates the HMGB1 levels (high mobility group box 1) which is protein regulate gene transcription and downregulates the JAK/STAT signaling pathway.	[126]
	Nude mice inoculate with A549-TPα cells	Reduces protein expression of thromboxane synthase (TxAS) and proliferating cell nuclear antigen (PCNA) alone or with cisplatin and reduces the toxicity and resistance of cisplatin.	[127]
	HCC827 pulmonary carcinoma cells.	Inhibits the onosteopontin expression (OPN), reduces the cells population in G2 phase and the proliferation and translocation potential and reduces MMP-2 and MMP-9 Expression.	[128]
isoliquiritigenin (14), isoliquiritin and Liquiritin (15),	A549 cell lines	Increase p53, p21 and Bax protein expression and downregulate AKT pathway. Also Inhibit cell cycle during the phase of G2/M and stimulate caspase 3 and 7.	[57]
Other cancer types			
Glycyrrhizinic acid	Human gastric carcinoma cells of SGC-7901, MGC-803 and BGC-823.	Induces apoptosis by Increasing cell cycle G1/S-phase arrest and by increasing levels of procaspase-3, -8, -9, Bax and PARP.	[54]
Glycrryhizin	B16 mouse melanoma cell line	Inhibits HMGB1 expression, suppresses epithelial-mesenchymal transition and inflammatory cytokines.	[129]
Isoliquiritigenin	HepG2 hepatocellular cancerous cells	Increases cell cycle G2/M phase arresting thus induce apoptosis and decreases cell growth.	[56]
Nigella sativa L.			
Lung cancer			
Alcoholic extract and oil of the seed	A549	educes cancer cells size and viability. The seed oil is more effective in lung cancerous cells than the extract.	[134]
Thymoquinone (16)	SCLC xenograft model H69, DMS79, H446, H841, and SW1271.	Reduces intracellular ROS levels, decreases tumor size and PARP in H446 SCLC, induces S-phase arrest in H69-adherent, H841-adherent, and SW1271 cells, with G1 arrest in DMS79 cells, as evidenced by a rise in cellular proportion in the related phases pertaining to the cell cycle.	[130]

Extract/isolated compound	**Cell line**	**Mechanism/ Action**	**Reference**
	A549	Reduces cancer cellular viability and proliferation.	[131]
	SCLC (CRL-5853 ATCC-NCI-H1048), malignant pleural mesothelioma (CRL-5820 ATCC-NCI-H28)	Reduces cell viability as Thymoquinone at 100 µM exhibited greater efficacy than cisplatin at 200 µM.	[132]
	A549	Induces apoptosis in lung cancerous cells via the stimulation of p53 and caspase cascade-dependent pathways.	[133]
Other cancer types			
Crude saponin extract	HCT116 colon carcinoma cells	Boosts the Bax/Bcl-2 ratio and reduces NF-κB and AP-1 proteins.	[135]
Ocimumbasilicum L.			
Lung cancer			
Basil extract	Human lung cancerous cell line (A549), human prostate cancerous cell line (PC3), and cervical cancerous cell line (HeLa)	Inhibits cancer cells growth.	[138]
Ethanol/Water extract	MCF-7 breast cell lines, NCI-H460 pulmonary carcinomacell lines, HeLa cervical carcinoma and HepG2 hepatocellular carcinoma.	Inhibits cancer cell growth and has Cytotoxic activity.	[136]

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Leaves	A549 pulmonary cancerous cells	Increases Baxproapoptotic protein, decreases Bcl-2 and increases the phosphorylation of ERK (extracellular signal regulated kinase) and AKT.	[137]
Maslinic acid (17)	A549 lung cancerous cells	Increases cytotoxicity by the HIF-1a signaling pathway and mitochondrial apoptotic pathway.	[139]
Other cancer types			
Aqueous extract	MCF-7 human breast cancerous cell line	Suppresses the development and proliferation of cancer cells, changes mitochondrial shape, inhibit oxidative stress genes and ROS production and increases the action of caspase-3.	[140]
		Inhibits the glycolysis pathway by inhibiting lactate production by MCF-7 cells. Dysregulates the Akt, mTOR and AMPK pathway.	[141]
Aqueous extract/ Eugenol	(MCF-7) cell lines	Aqueous extract Reduces cellular growth and Eugenol Increases P53 and decreases bcl-2 gene expression causing apoptosis.	[60]
Eugenol (18), Isoeugenol	Cell line of salivary gland	Induce the apoptosis of cancerous cells and promote suppression of DNA synthesis and exhibit significant cytotoxic action against tumor cell lines.	
Essential oil	Glioblastoma (U-87 MG), (MDA-MB-231) and ER+ breast cancer (MCF7) cell lines.	Potent antitumor activity	[142]
Panax ginseng L.			
Lung cancer			
Ginsenosides Rb1(19), Rb2 (20) and Rg1 (21)	A549, NCI-H358 and NCI-H596	Decrease cancer cellular viability and proliferation, Rb1, Rb2 and Rg1 increase caspase 3, 8 expressions so induce apoptosis.	[146]
Ginsenoside Rg3-fortified red ginseng preparation (Rg3-RGP) (22)	H460 and nude mouse xenograft model	Decreases tumor mass and growth and has cytotoxic activity to cancer cells due to its metabolites-mediated immunopotentiation.	[147]

Extract/isolated compound	**Cell line**	**Mechanism/ Action**	**Reference**
Modified regular ginseng extract	A549, H1299 and H596	Decrease cancer cells growth. In A549: causes arresting at G2/M phase, modulates AMPK by downregulating mTOR and 4EBP1 and stimulates autophagy.	[144]
Panaxydol (23)	A549 and NCI-H358	Causes cell cycle G1 phase arrest through the control of G1-mediated protein expression and up-regulates Ca2+.	[143]
xl, 1c and 8b (25-hydroxyprotopanaxadiol derivatives)	A549 and H460	Inhibit cellular growth and migration, induce apoptosis, causes cell life cycle G1/S phase arrest and decrease ß-catenin signaling pathway.	[145]
Other cancer types			
Rh2 (24)	U20S osteosarcoma cells	Inhibits cellular proliferation by suppressing phosphatidylinositol 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway.	[63]
Rp1	MCF-7, MDA-MB-231, MCF-7/ DOX and T-47D breast cancerous cells.	Induces arresting cell cycle and apoptosis-mediated suppression of cell proliferation.	[148]
Rosmarinus officinalis L.			
Lung cancer			
Carnosic acid (25) and Rosmarinic acid (26)	A549, H1299 and H460	Modifies the activation and expression of AMPK, Akt and ERK signaling molecules that control cellular proliferation and survival.	[68]
Hydroalcoholic extract	A549 lung cancerous cells	Inhibits cancer cells proliferation and rosmarinic acid had strongly binding interaction with the target proteins c-Src and FAK thus, decrease the overexpression of NSCLC proteins.	[149]

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Methanolic extract	H1299 NSCLC cells	Induces apoptosis by inducing ERK and AMPK signaling so inhibits the mTORC1 activity and impedes migration and proliferation of cancer cells.	[150]
	A549 cells	Induces apoptosis by reducing mTOR, AkT and p70S6K levels.	[151]
Supercritical extract	NCI-H1299 (H1299) and NCI-H1975 (H1975)	Decreases Lipid metabolism-associated genes in NSCLC and cellular proliferation when combined with cisplatin, pembrolizumab or pemetrexed.	[152]
Other cancer types			
Ethanolic extract/ Carnosol (27)/ Rosmarinic acid	Human ovarian carcinoma A2780 and cisplatin resistant A2780CP70 cells	Increases antiproliferation activity when combined with cisplatin and causes apoptosis by affecting cell cycle and genes control apoptosis. Carnosol and Rosmarinic acid showed synergistic effect on A2780 cell lines with cisplatin.	[154]
Methanolic extract	PC-3 prostate cancerous cells	Decreases the survival, proliferation and migration, also decreases mTOR and Aktsignaling so induces apoptosis.	[153]
Salvia officinalis L			
Lung cancer			
1,8-cineole (28), α-thujone and Camphor (29)	A549 and NCI-H226 Human lung cancerous cell lines	Decrease proliferation effect due to synergistic effect.	[158]
Cirsiliol (30), luteolin (31), and carnosol	HepG2 cells and A549 cells	Inhibit STAT3 signaling thus, impede the development and multiplication of cancerous cells.	[72]

Extract/isolated compound	**Cell line**	**Mechanism/ Action**	**Reference**
Ethanolic extract	A549 lung cancerous cell line and Ninety Swiss Albino rats.	In vitro: Increases cancer cells cytotoxicity In vivo: increase gene expression of AKT, P53, Bcl-2, Bcl-XL, and vanin-1.	[69]
Hydroalcoholic and aqueous extract	A-549, A-375, Hep-2, HeLa and HT-29 cell lines.	Induce apoptosis and cytotoxic activity.	[156]
Methanolic extract	Lung A549, prostate PC3, breast MCF7 and liver HepG2 cancer cells.	Potent toxicity on cancerous cells specially lung cancer	[155]
Ursolic acid (32) and pomolic acid (33)	NCI consisted of a series of NSCLC, colon cancer, renal cancer, ovarian cancer, tumor cells in the central nervous system, leukemia, melanoma, prostate carcinoma, and breast cancer.	Target NF-κB pathway to inhibit NF-κB-mediated functions thus has anticancer activity.	[157]
Other cancer types			
Aqueous extract	Rats with colon cancer	Reduces DNA damage caused by oxidative H_2O_2 stress	[71]
Essential oil	A375, A2058 and M14 human melanoma cell lines	Induces apoptosis and reduce adverse effects in cancer patients.	[159]
Thymus vulgaris L.			
Lung cancer			
Essential oil	H460 (non-small-cell lung cancer cells), CF-7 breast cancer and MOLT-4 (human lymphoid cell lines).	Increase antiproliferative activity.	[76]
Ethanolic extract	H460 lung cancerous cell line and (HBEpC/HTEpC) normal cells.	Reduce NF-kB p65 and NF-kB p52 proteins expression and altered the liberation of IL-1 beta and IL-8.	[161]

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Thymol (34)	A549 cell lines.	Induce apoptosis, mitochondrial membrane depolarization and leads to arrest at the G0/G1 phase of the cell cycle.	[75]
Thymoquinone/Water-methanol extract	(A549) and (BEAS-2B) normal human parochial epithelial cell.	Reduce DNA oxidative damage induced by H2O2 in cancerous lung cells.	[160]
Other cancer types			
Essential oil	MCF-7 and MDA-MB-231 cells.	Causes anti-CSC, anti-proliferative, antiangiogenic, antioxidative, and proapoptotic effect.	[163]
	Head and neck squamous cell carcinoma (HNSCC), UMSCC1.	Induces N-glycan biosynthesis, interferon signaling and extracellular signal-regulated kinase 5 (ERK5) signaling.	[164]
Ethanolic extract	THP-1 cell line monocyclic leukemia.	Reduces cellular viability and causes cytotoxicity to cancer cells.	[166]
Naringenin (35)	Human breast cancerous cell lines (HTB26, HTB132), Human colorectal cancerous cell lines (SW1116 and SW837) and normal human fibroblast cells (CRL1554).	Causes arresting the cell cycle during the S- and G2/M phases, which is accompanied by a rise in apoptosis and increases caspases 3, 7, 8 and 9, AIF, Bak and Bax expression.	[165]
Thymol	HCT116 and Lovo colorectal cells.	Causes apoptosis and cell cycle arrest. Suppress the Wnt/β-catenin signaling pathway.	[162]
Trigonellafoenum-graecum L.			
Lung cancer			

Extract/isolated compound	**Cell line**	**Mechanism/ Action**	**Reference**
Diosgenin (36)	A549 lung cell lines.	Inhibits telomerase activity through the reduction of hTERT gene.	[170]
Ethanolic and aqueous extract	lung (A-549), colon (HT-15, HT-29) and neuroblastoma (IMR-32).	Inhibit the growth of cancerous cells hence has anticancer activity.	[169]
Ethyl iso-allocholate (37)	A546 lung cancer cell and zebrafish.	Promotes apoptosis through the activation of the caspasesignaling pathway in A549 cells and reduces tumor proliferation, hepatic metastasis, and angiogenesis in zebrafish.	[168]
Methanolic extract	A549 lung cell line.	Increases caspase 3 expression thus decreasing the cancer development, reducing cellular viability and lipid peroxidation.	[167]
Other cancer types			
Aqueous extract	(L20B) female intestine of albino mice cell lines and (RD) Rhabdomyosarco mase in human cell line.	Increases cytotoxic activity thus, has Anticancer activity.	[173]
	Vero cell line (CCL-81).	Decreases the adverse effects of cisplatin when combined with cisplatin.	[174]
Methanolic extract	HCT8 cell line of colorectal, KAIMRC1 breast cancerous cell line, HL60 leukemia cell line, MDA-MB-231 breast cancerous cell line, and HCT116 colorectal cancerous cell line.	Reduces tubulin polymerization.	[171]
	MCF-7 and SK-BR3 Breast cancerous cell.	Increases ROS, mitochondrial depolarization and Bax/Bcl-2 ratio via p53 signaling pathway and stimulates apoptosis.	[172]
Zingiber officinale L.			
Lung cancer			

Extract/isolated compound	Cell line	Mechanism/ Action	Reference
Ethyl acetate fraction	A549 lung cancerous cell lines.	Down-regulates hTERT and though down-regulates c-Myc which are cancer specific targets and reduces telomerase activity.	[177]
6-Gingerol (38)	Six-week-old female ICR mice and The Lewis lung carcinoma (LLC) cells.	Decreases the quantity and smaller size of pulmonary cancer nodes and rises the proportion of M1 macrophages.	[175]
6-paradol (39) and 6-shogaol (40)	A549 cells.	Inhibits hTERT expression and telomerase activity.	[83]
6-shogaol	NCI-H1650 lung cancerous cells.	Induces apoptosis and suppresses proliferation by downregulating AKT signaling.	[176]
Other cancer types			
Ethanolic extract	HCT116 and HT29 colon cell lines.	Increases caspase 3 and BAX protein expression, cell cycle G0/G1 phase arrest and decreases Bcl-2 protein thus, induces apoptosis.	[179]
Ethanolic extract to form Bi2O3 nanoparticles	HCT116 colorectal cancerous cells.	Reduces The expression of mRNA for PI3K, mTOR and AKT so induce apoptosis through PI3K/AKT/mTORsignaling pathway.	[181]
Ethanolic extract	MCF-7 and MDA-MB-231 breast cancerous cells.	Inhibits both c-Myc and hTERT which are specific targets for cancer cells, and can activate apoptosis	[180]
6-gingerol, 6-shogaol	MCF-7 breast cancerous cell line.	Inhibits the mTOR expression at mRNA and protein levels thus, decrease metastasis and proliferation when combined with Terminaliachebula extract.	[178]
6-gingerol, 6-paradol, 6-shogaol and zingerone	Dalton's lymphoma ascites on Swiss albino mice.	Decrease levels of tumor enzymes AST, ALT, ALP, and γ-GT thus, may serve as antitumor agent.	[182]
Root tincture nano emulsion	Prostate cancerous cell line (PC3) and skin fibroblasts (HFF).	Increases the radical scavenging activity and arresting the cell life cycle during S and G2/M phases thus, induce apoptosis.	[81]

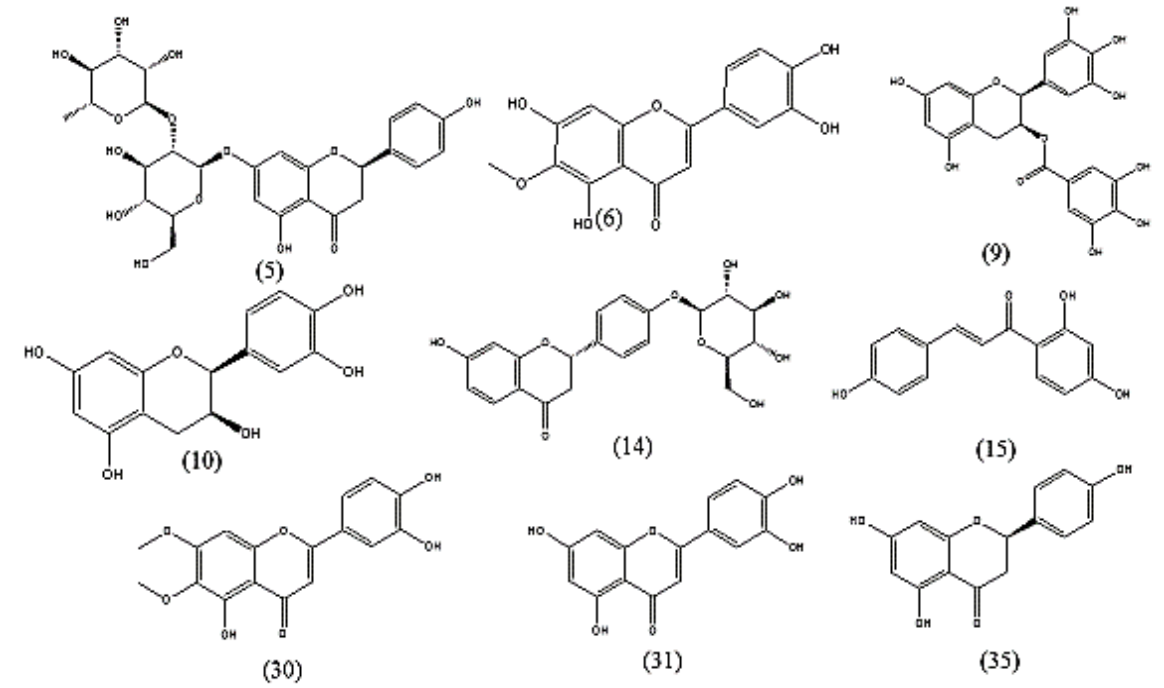

Figure 1:Flavonoids with anticancer activityin some selected plants

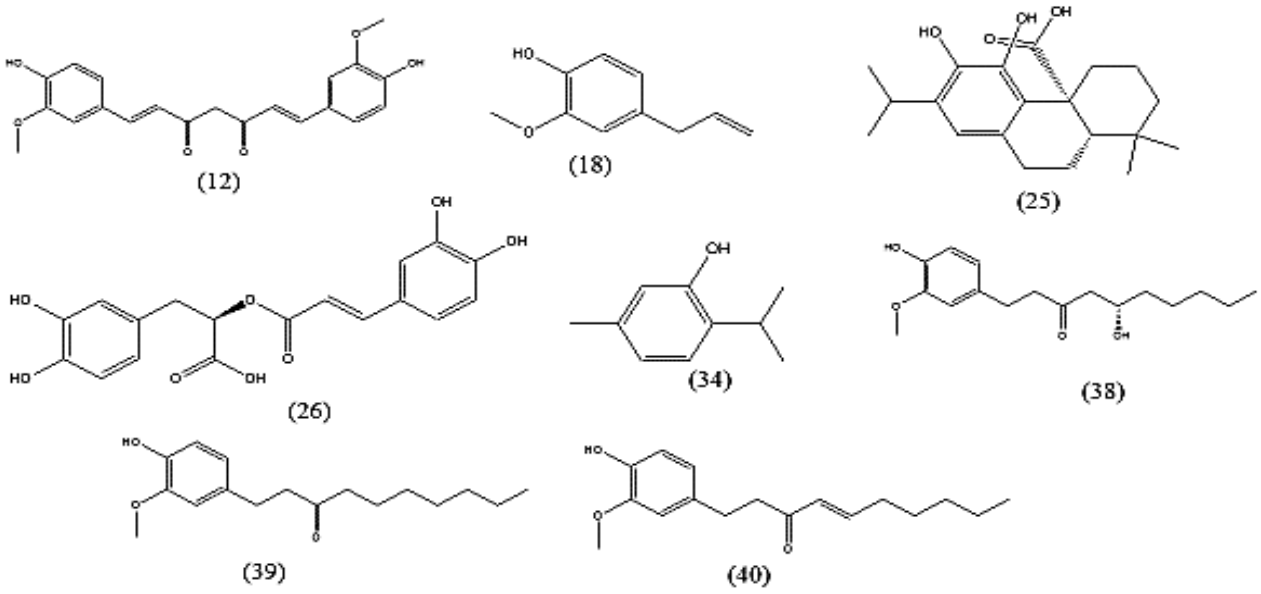

Figure 2: Phenols with anticancer activityin some selected plants

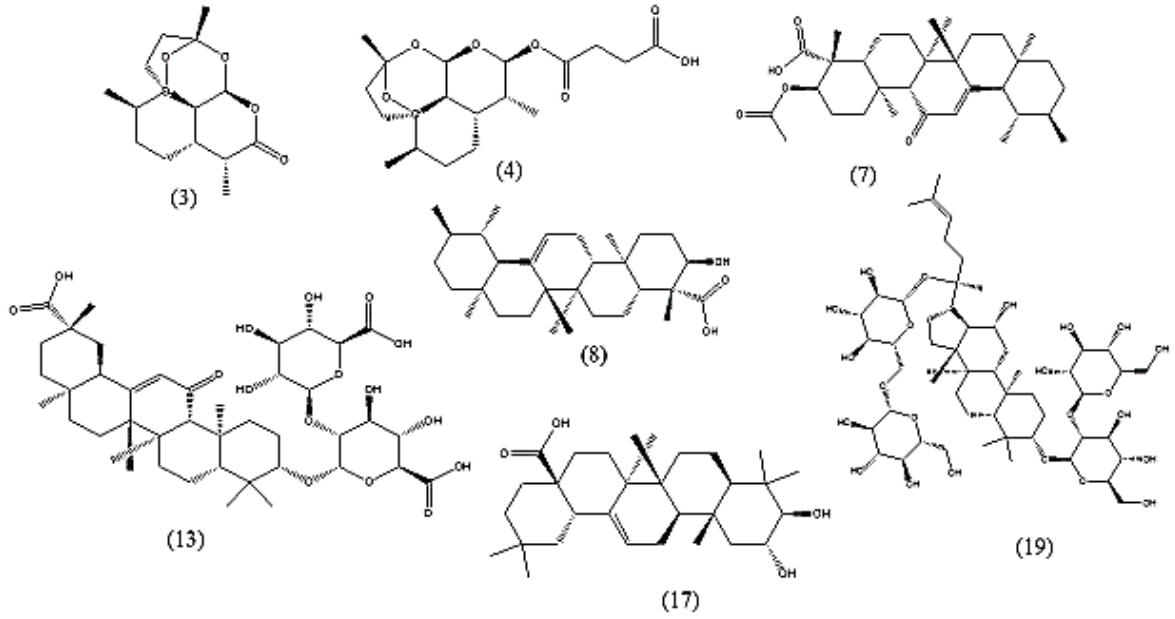

Figure 3a: Terpenes with anticancer activityin some selected plants

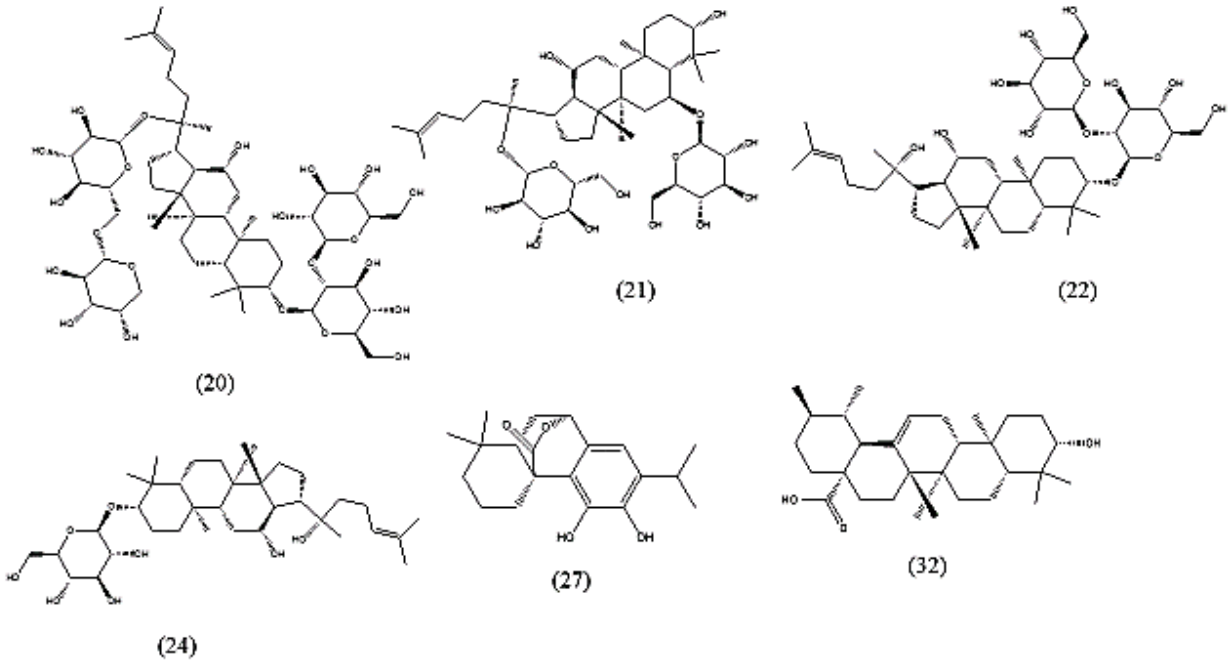

Figure 3b: Terpenes with anticancer activityin some selected plants

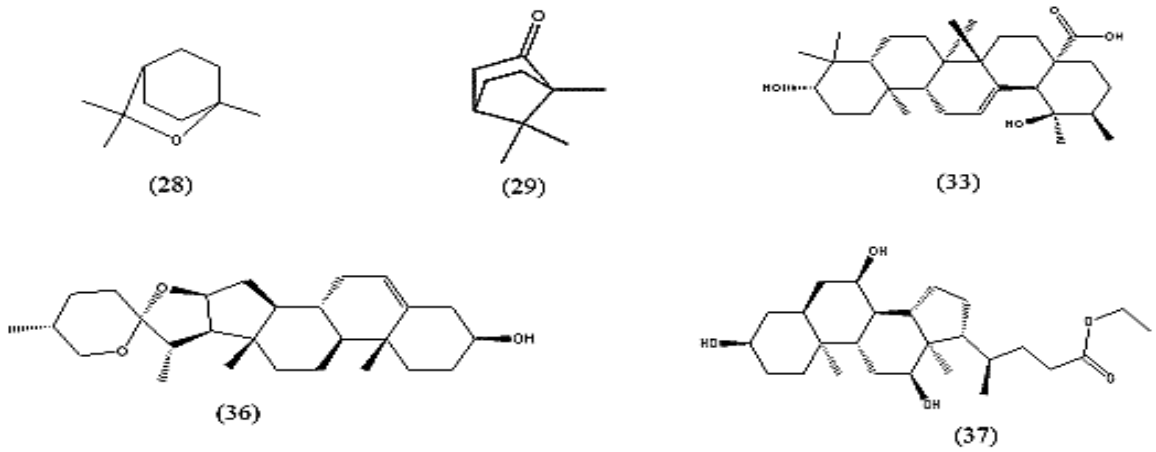

Figure 3c: Terpenes with anticancer activityin some selected plants

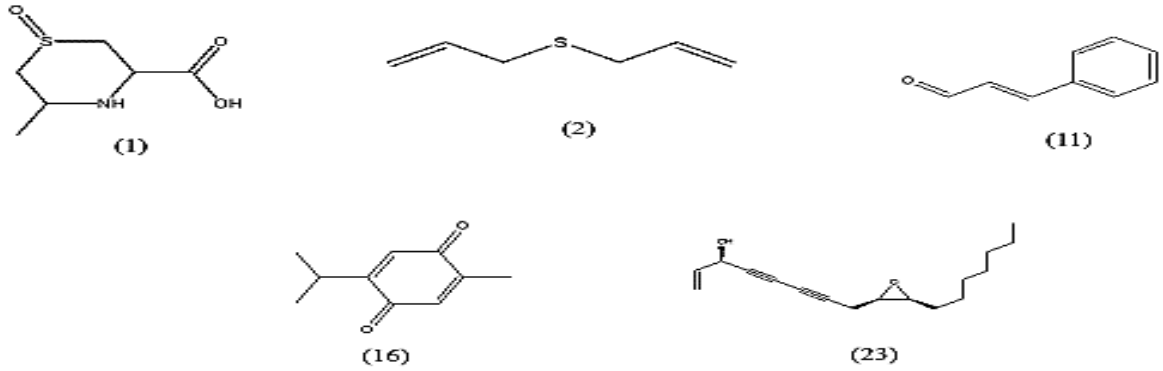

Figure 4: Miscellaneous compounds with anticancer activity.

Conclusion:

In conclusion, employing natural plants in lung cancer treatment offers a promising and complex strategy, addressing the disease through many biological processes including apoptotic induction, cell cycle arrest, anti-angiogenesis, and autophagy. Plenty of natural plants have anticancer properties against NSCLC as A549 cancerous cell lines due to their phytochemical content as artemisia, basil, cinnamon, fenugreek, frankincense, green tea and others reported in the review. Mixture of natural plants extracts may be combined with chemotherapy to induce its activity or decrease its side effects thus improve cancer patient's life quality. Incorporating natural products into conventional oncology may yield more effective, tailored, and comprehensive approaches for lung cancer treatment.

List of abbreviations

Abbreviation	**Word**
(Ak)	Serine/threonine kinase
(APAF1)	apoptotic protease-activating factor1
(BAD)	BCL2 associated agonist of cell death

Abbreviation	Word
(Bak)	Bcl-2 homologues antagonist/killer
(Bax)	Bcl-2-associated protein x
(Bcl-2)	B-cell lymphoma 2
(Bcl-xL)	B-cell lymphoma-extra large
(Bcl-Xs)	B-cell lymphoma short isoform
(Bfl-1)	Bcl-2 related gene expressed in fetal liver
(BH3)	interacting-domain death agonist
(Bik)	Bcl-2-interacting killer
(Bim)	B-cell Lymphoma 2-like protein
(c-myc)	Cellular myelocytomatosis viral oncogene homolog
(COX)	Cyclooxygenases
(EC)	(-)-epicatechin
(EGCG)	Epigallocatechin-3-gallate
(EGFR)	epidermal growth factor receptor
(egr-1)	early growth Response Gene 1
(G0)	Resting phase
(G1)	Gap phase 1
(G2)	Gap phase 2
(HDGF)	hepatoma-derived growth factor
(HRK)	Harakiri BCL2 Interacting Protein
(hTERT)	human telomerase reverse transcriptase
(hTR)	human telomerase RNA
(JNK1)	C-Jun N-terminal protein kinase 1
(LOX)	Lipoxygenases
(M)	Mitosis phase
(MAPK)	Mitogen-activated protein kinase
(MCL-1)	Myeloid cell leukemia-1

Abbreviation	Word
(MOMP)	Mitochondrial outer membrane permeabilization
(mTOR)	mammalian target of rapamycin
(Noxa)	phorbol-12-myristate-13-acetate-induced protein 1
(NSCLC)	non-small cell lung cancer
(PD-L1)	programmed cell death ligand 1
(PI3K)	phosphatidylinositol 3-kinase
(PTEN)	phosphatase and tensin homolog
(PUMA)	p53-upregulated modulator of apoptosis
(RTK)	receptor tyrosine kinase
(SCLC)	small cell lung cancer
(SFRE)	Supercritical extract Of rosemary
(TKI)	Tyrosine kinase inhibitors
(TQ)	Thymoquinone
(VEGFR)	vascular endothelial growth factor receptors
(Wnt)	Wingless-related integration site

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