Rahimlouy Aghdam and Hamedeyazdan, ***BioImpacts.*** 2025;15:30074
doi: 10.34172/bi.30074
https://bi.tbzmed.ac.ir/

Promising leads against lung cancer from the plants in Lamiaceae family

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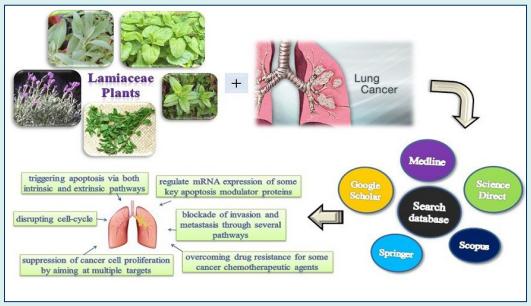
Article Info

Article Type:
Review

Article History:
Received: 27 Aug. 2023
Revised: 6 Jan. 2024
Accepted: 6 Feb. 2024
ePublished: 8 Jun. 2024

Keywords:
Apoptosis
Gene expression
Lamiaceae
Medicinal plants
mRNA
Phytochemicals

Abstract



Introduction: Ceaselessly, management of cancer has been the major global challenge for healthcare professionals. As regards, lung cancer (LC) has been introduced as the second most common form of cancer in both men and women, taking the lives of more than a million people each year, statistically holding the highest mortality rate among all cancer types. Although much effort has been made for the management of LC, current therapies are quite ineffective. With reference to the fact that the most current chemotherapeutic agents for LC are of plant origin, the authors hereby collected the acclaimed plants from the Lamiaceae family which have shown remarkable activity against LC.

Methods: The incorporated papers were published between the years of 1997 and 2023. The principal search keywords for this review article were "lung cancer", "Lamiaceae", "cytotoxic effect", "anti-tumor" and "anti-proliferative" in Medline, Springer, Scopus, ScienceDirect and Google Scholar databases.

Results: To the furthest extent, different responsible mechanism(s) of action for the anti-cancer properties of each plant are discussed. The respected IC_{50} values for plant extracts, essential oils or pure isolated compounds are underlined as well.

Conclusion: Many plants and isolated relative phytochemicals have shown exceptional anti-cancer potency against LC; nonetheless, they still remain undisclosed. We believe that this assembled data would globally inspire scientists on the passing way of LC treatment.

Introduction

Declaredly, lung cancer (LC) is reported to be the leading cause of cancer incidence and cancer associated deaths.[1] Threatening the lives of above two million people worldwide annually, LC places the second frequent cancer in men after prostate malignancy, and the top in women after breast cancer. LC was reported to be the leading cause of cancer mortality in 93 nations, involving China, Russia and the United States of America[2] which is estimated to account for 127 000 deaths by the end of 2023 merely in the US.[3] Principally, LC comprises of small cell LC (SCLC) and non-small cell LC (NSCLC). Statistically, only 13% of all LC patients are SCLC cases, and majority of them (84%) are classified in NSCLC group.[1] Plant kingdom has been a well-known essential source of novel therapeutic agents against cancer.[4] The prevailing chemotherapeutic agents have several therapeutic limitations since they affect healthy tissues, causing myriad health problems and adverse side effects; hence, there has been an escalating demand for alternative treatments. Naturally-derived anti-cancer agents obtained from plants have been an appealing source in the last decades. The secondary metabolites of plants have been investigated for their potential anti-cancer effects for many years. They have been shown to possess anti-cancer activities mainly by induction of apoptosis, inhibition of cancer cell growth, cancer cell cytotoxicity and by exerting antioxidant properties.[5] A plant family of certain interest is Lamiaceae, which comprises several genera with substantial anti-cancer properties that have been found to have prominent potential against colon, lung, prostate and breast cancer cells in *in vitro* studies. Taken together, they

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enforce their cytotoxicity by selectively organizing cancer cell death, especially via apoptosis induction; Some were found to influence angiogenesis, as well.[6] The majority of Lamiaceae family plants are essentially well-recognized for their aromatic properties. Pharmacological findings have uncovered that the essential oils (EO) of Lamiaceae plants also possess anti-cancer properties. Likewise, it has been reported that Lamiaceae plants comprise a diverse content of phytochemicals, predominantly consist of phenolic compounds, like flavonoids or benzoic acids, terpenoids and steroids.[7] Regarding the progressing incidence of LC alongside the impressive worth of medicinal plants from the Lamiaceae family, the authors hereby aimed to compile and review the online literature upon plants of Lamiaceae family which have displayed remarkable *in vitro* and *in vivo* activities against LC. There have been many promising lead compounds against LC isolated from the plants of Lamiaceae family; thus far, many are self-abandoned and quite unlearnt that demand more investigations to lead to an exquisite, operational medicine. We trust that the collected data could assist experts all across the world in searching for new active phytochemicals against LC. It is assumed that this review could assist and inspire scientists and researchers in the path of LC treatment.

Methods and Materials

We have included each studied plant of Lamiaceae to date that has been reported to exhibit activity against LC whether in *in vitro* or *in vivo* studies. Some of the plants with very minor or ignorable cytotoxicity were excluded from this review. The papers with invalid registration properties or lacking proof of proficiency were also excluded. The incorporated papers were published between the years of 1997 and 2023. The main search keywords for this review article were "lung cancer", "Lamiaceae", "cytotoxic effect", "anti-tumor" and "anti-proliferative" in Medline, Springer, Scopus, ScienceDirect and Google Scholar databases.

Plants with anti-cancer properties

In this section, the promising findings regarding LC from the studied plants are briefly described. The chosen plants are represented with no specific arrangement and are randomly ordered. The suggested mechanisms of plants anti-cancer features are detailed to the furthest extent. As a final point, the anti-cancer potency indicators (such as IC_{50s}) for each plant and a summarized content of the reviewed studies are tabulated separately.

Phlomis younghusbandii

A significant anti-inflammatory activity was reported from Phlomisoside F (PMF), an isolated glycoside from ethyl ethanoate extract of *P. younghusbandii* roots.[8,9] Lu *et al* confirmed the growth inhibitory impact of PMF on a NSCLC cell line, known as A549 cells. They reported that PMF restrained A549 cells invasion and migration (known as metastasis) in a time and concentration dependent manner.[10] Apoptosis, one of the main mechanisms of cytotoxic activity of phytochemicals, can be provoked by both intrinsic and extrinsic pathways.[11] The release of specific mitochondrial proteins is in charge of triggering the intrinsic apoptosis pathway; on the other hand, the extrinsic corridor is activated mainly by death receptors.[12,13] A protein known as caspase-8 (cas-8) plays an important role in the extrinsic apoptosis pathway. In contrast, the activated cas-9 is a key factor in activation of the intrinsic pathway.[11] Both activated cas-8 and cas-9 can set off executioner caspases like cas-3 which will arouse death substrates and conclusively lead to apoptosis.[14] It has been reported that expression of cas-3 and cas-9 are often restrained in cancer cells, including LC. Moreover, the B-cell lymphoma 2 (Bcl-2) protein families are an effective regulator of proapoptotic proteins release. Bcl-2 is a key anti-apoptotic protein, thus Bcl-2 overexpression leads to cell survival. Furthermore, Bcl-2-associated X protein (Bax), a pro-apoptotic member of Bcl-2 family, could essentially play a role on the mitochondrial membrane.[15] Lu *et al* reported PMF to boost cas-3, cas-9 and Bax expressions while reducing Bcl-2 expression; thus, PMF provoke apoptosis in A549 cells via a mitochondria-mediated pathway. In addition, cyclooxygenase 2 (COX-2), a strategic enzyme in arachidonic acid metabolism, could enhance prostaglandin E2 (PGE2) formation.[16] It was witnessed that PGE2 can increase Bcl-2 and interleukin-6 (IL-6) production, resulting in apoptosis inhibition; hence, exacerbating cancer progress.[17] COX-2 and PGE2 can hasten LC development as elevated levels of COX-2 are frequently attested in LC patients.[10] PMF could efficiently downgrade COX-2 expressions in A549 cells, signifying that this might be an alternative anti-cancer influence of PMF on LC.[10]

Scutellaria baicalensis

Baicalin, baicalein, oroxylin A, wogonin, wogonoside are deemed as chief constituents of *S. baicalensis* which were mainly obtained from plants' roots and exhibited significant anti-cancer effects.[18] *S. baicalensis* were studied in terms of signaling pathways and potential targets regarding LC; including suppression of proliferation by restraining the cell-cycle, apoptosis stimulation, blockade of cancer metastasis and overcoming drug resistance as well.[18] Li *et al* compared the anti-tumor effects of *S. baicalensis* with cisplatin in four tumor xenograft models (A549, Lewis lung carcinoma (LLC), and two other human LC cell lines known as H460 and H411) and reported that the tumor inhibitory rate of *S. baicalensis* were almost neighboring the obtained results from cisplatin. Remarkably, baicalein and baicalin were more potent than cisplatin in H411 and H460 tumor models.[18]

S. baicalensis has already established a good reputation in Chinese medicine as an adjuvant to chemotherapy in LC treatment. Anti-cancer studies confirmed that crude ethanol extracts of *S. baicalensis* were selectively toxic to A549 and a human lung adenocarcinoma cell line known as SK-LU-1 cells.[19] Flavones of *S. baicalensis* have been reported to cease various cancer cell lines, including NSCLC.[20] *In vivo* studies approved that treating H460 and A549 cells with baicalein, baicalin, and wogonin resulted in anti-proliferation and anti-angiogenesis impacts mainly by reducing expressions of inhibitors of differentiation 1 (Id1) protein, the epithelial-mesenchymal-transition (EMT)-related molecules (such as vimentin and N-cadherin), fibroblast growth factor receptor 2 (FGFR2) and vascular endothelial growth factor A (VEGF-A).[20,21] Park *et al* confirmed that the aqueous extract of *S. baicalensis* roots inhibited A549 cells growth and induced cell cycle arrest at G1 phase by downregulating cyclinD1, cyclin-dependent kinase 4 (CDK4) and matrix metallopeptidase (MMP) 2 productions.[22] Moreover, Kim *et al* reported induced apoptosis in NSCLC cell lines H2087 and H358 following treatment of the aqueous extract of *S. baicalensis* roots. The reported anti-cancer mechanisms were described as increasing cas-3 and phospho-AMP-activated protein kinase (AMPK), reinforcing poly ADP ribose polymerase (PARP) cleavage and decreasing mammalian target of rapamycin (mTOR).[23] Wang *et al* investigated the cytotoxic effects from ethanol extract of *S. baicalensis* roots on A549 cells; where, the extracts upregulated expression of p53 and downregulated expression of cyclinD1; resulting in malignant cells detention.[24] Furthermore, Gao *et al* reported that the ethanol extracts of *S. baicalensis* affected NSCLC cells by inducing apoptosis via downregulating expressions of cyclinA and upregulating expressions of p53 and Bax.[19] Gong *et al* studied the toxic effects of the obtained extracts from *S. baicalensis* on two nicotine-induced NSCLC cell lines, A549 and H1299; all the extracts were reported to upregulate the expression of Bax and downregulate MMP2, MMP9, cas-3, bcl-2 and bcl-2/bax ratio. The extracts also accompanied anti-inflammatory activity in NSCLC cells by reducing expressions of nuclear factor kappa light chain enhancer of activated B cells (NF-κB), TNF-α, I-kappa B-alpha and IL-6.[25] Zhao *et al* reported the effects of isolated flavonoids baicalin, baicalein and wogonin from this plant on H1299 and A549 cells; where, growth, invasion and migration of NSCLC cells were extremely restrained.[26] They suggested that the combination of chemotherapeutic agents and flavonoids might be a prospective strategy for increasing the anti-cancer potential of LC treatment.[20] Another study revealed that first-generation epidermal growth factor receptor tyrosine kinase inhibitors known as EGFR TKIs, as erlotinib and gefitinib, substantially lessened tumor growth and expanded survival rate of NSCLC patients. Despite the valued merit of these drugs versus cancer, resistance develops less than a year after treatment begins. Ethanol extract of *S. baicalensis* diminished cell growth and induced apoptosis in EGFR TKI-resistant human NSCLC cell lines by suppressing STAT3 activity[27]; consequently, it was put forward that the potential use of *S. baicalensis* as a novel therapeutic agent for LC patients with EGFR TKI resistance could be a promising lead.

Scutellaria barbata

There have been numerous reports regarding the anti-cancer effects of obtained extracts from *S. barbata*. A Study contended that ethanol extracts of *S. barbata* (SB) greatly inhibited A549 cells proliferation with IC_{50} of 0.21 mg/mL. The chief mechanism of action was reported as provoking apoptosis.[28] In line with reports, Scutebarbatine-F, a diterpene alkaloid from SB, exhibited good cytotoxicity versus a range of human tumor cells. In addition to Scutebarbatine-F, SB was also reported to contain wogonin, baicalein, scutellarin, ursolic acid and b-sitosterol; all reported to have significant anti-tumor activities.[29] These promising anti-cancer compounds could be the key components for NSCLC treatment, considering that they are positively aiming for a number of targets such as Bax, iNOS, and P38.[29] *In vitro* studies further confirmed that baicalein oppose NSCLC via regulating certain vital proteins including COX-2, NF-κB, Bax, extracellular signal-regulated kinase (ERK) and CDK1.[29] *In vivo* anti-tumor activity of baicalein were also studied, confirming baicalein as a considerable anti-cancer nominee for LC.[29] The results of another study supported the significant cytotoxic effects of SB on particular LC cell lines which were remarked with IC_{50}s between 0.1-0.8mg/mL. The suggested anti-cancer mechanisms were as a result of multiple apoptotic pathways regulations, involving p53 activation and/or EGFR inhibition.[30] Additionally, the isolated polysaccharides from SB have been reported to have anti-tumor effects as well. An extremely invasive and metastatic LC cell line, 95-D, was treated for exploring the underlying mechanism(s). The results indicated that these polysaccharides directly regulated the c-Met signaling pathway and the anti-tumor effects were mainly due to their anti-proliferation and anti-angiogenesis properties.[31] Furthermore, hypoxia-induced factor 1-alpha (HIF-1α) is a transcription factor that increases invasion in cancer cells by stimulating the metastasis-related gene expression in hypoxic conditions. SB was reported to lessen the HIF-1α expression level and VEGF secretion in cancer cells; consequently, leading to its anti-angiogenesis effects.[32]

Melissa officinalis

The tiniest analyzed concentrations of lemon balm leaves extract were reported to considerably reduce the viability of A549 cells.[33] It has been reported that *M. officinalis*

enforce anti-cancer activity on multiple cancer cell lines, including LC. The active anti-cancer components of *M. officinalis* demonstrate their cytotoxic effect through several mechanisms including anti-proliferation, anti-angiogenic, anti-apoptotic, cell cycle arrest, and by possessing antioxidant properties.[34] In a survey by Jahanbin *et al*, *M. officinalis* aqueous extract significantly downregulated telomerase reverse transcriptase (hTERT) and VEGF-A in A549 cells indicating that *M. officinalis* exerted its anti-proliferative effects partially via parallel downregulation of both hTERT and VEGF-A expressions.[35] *M. officinalis* prevents angiogenesis, which is via inhibition of MMP9 and VEGF. Besides, expression levels of neovascularization elements such as FGF-2, MMPs (MMP9 and MMP2), and VEGF-A, -B, -C, -D declined as a result of *M. officinalis* treatment.[36] Notably, high anti-angiogenic activity of *M. officinalis* was linked its excessive anti-telomerase activity. It was concluded that the alteration of hTERT and VEGF-A gene expressions can be considered as a common target in LC.[35] Moreover, *M. officinalis* displayed a powerful free radical scavenging potency, as much as 10 folds greater than vitamin C.[37] Elsewhere, an *In vivo* study on rats revealed that oral ingestion of *M. officinalis* extracts sustained histologic properties of heart tissue cells following doxorubicin-induced damage. Sousa *et al* investigated the effects of *M. officinalis* EO on A549 and four other cancer cell lines. It was attested that EO possess significant antioxidant potential.[37,38] Moaca *et al* studies concluded that rosmarinic acid (RA) a well-known phenolic compound from *M. officinalis* was responsible for the plants anti-migratory effects.[39,40] Jahanban-Esfahlan *et al* evaluated the anti-tumor effect of Lemon balm different extracts, on H460 and two other cancer cell lines; reporting the ethanol extract as the most effective, and H460 cell line as the most affected cells.[35] They concluded that *M. officinalis* dose-dependently affected the cell cycle profile of H460 cells. By scrutinizing the expression levels of the proteins engaged in cell cycle and apoptosis, it was revealed that proteins responsible for triggering apoptosis, such as p53, cytochrome C, and Bax intensified upon *M. officinalis* ethanol extract treatment. The apoptotic activity of Bcl-2 protein can be regulated by p53 as a tumor suppressor protein. Subsequently, cytochrome C was found to endorse the caspase cascade. These proteins regulated apoptosis via mitochondrion permeability alteration.[34] The results of another study confirmed that among all the studied *M. officinalis* extracts and cancer cell lines, the ethanol extract presented the highest anti-tumor activity and H460 cells were reported as the most sensitive cells. Treating the H460 cells with ethanol extract followed a reduction in pro-cas-3 and an upsurge in p53 expressions.[41] Cytotoxicity of different doses of *M. officinalis* extracts towards different cancer cell lines including A549 cells was evaluated by Jahanban-Esfahlan *et al* where, in all assessed cancer cell lines, *M. officinalis* extract reduced the cell viability to values below 33% (all the obtained IC_{50} values were remarkably below 5μg/mL). The average growth inhibition of A549 cells was reported to be 77.8%.[42]

Ocimum gratissimum

Chen *et al* investigated the cytotoxic effects of aqueous extract of *O. gratissimum* (OGE) on A549 cells and the alterations provoked by OGE in these cells. It was discovered that OGE dose-dependently decreased the viability of A549 cells via inducing DNA condensation, resulting to cell shrinkage. Other parallel studies reported that OGE boosted initiation of cas-3, cas-9 and cas-8 and raised apoptotic peptidase activating factor 1 (Apaf-1) and Bcl-2 antagonist killer 1 (Bak) protein levels; contrarily, OGE declined Bcl-2 expression. In addition, OGE hindered the phosphorylation of ERK; however, it enhanced the phosphorylation of p38 MAP kinase and c-Jun N-terminal kinase (JNK). In conclusion, Chen *et al* contended that OGE treatments considerably dropped A549 cells viability by affecting both wings of apoptotic and anti-apoptotic pathways through a combined effect of provoking apoptotic signaling and suppressing the anti-apoptotic signaling.[43] Cytotoxicity of oleanolic acid isolated from *O. gratissimum* has been investigated against six cancer cell lines including A549; where, oleanolic acid exhibited bioactivity against all studied solid tumor cell lines.[44] Elsewhere, OGE induced apoptosis in A549 cells by modulating some cell cycle regulators and apoptosis-related factors, concerning with drug resistance.[45]

Ocimum sanctum

The chemopreventive effects of *O. sanctum*, Tulsi, have been evidently reported through the past Studies. Previous studies confirmed that Tulsi prevented LC by different mechanisms of action such as possessing antioxidant activity, inducing apoptosis and preventing neovascularization.[46] The effect of ethanol extract of *O. sanctum* (EEOS) in A549 cells was studied; where, it substantially reduced the extracellular connection of A549 cells, leading to cell death. EEOS induced DNA condensation as well. Furthermore, EEOS was able to induce apoptosis via up-regulation of cas-3 expression, increased reactive oxygen species (ROS) production, and diminished Bcl-2 activity. Moreover, EEOS also blocked expressions of superoxide dismutase 2 (SOD2) and glutathione peroxidase (GPx). In brief, these results proved that EEOS encouragingly was active against A549 cells through different mechanisms.[47] Elsewhere, the cytotoxic activity of EEOS in H460 cells was evaluated *in vitro*; it was seen that with higher concentrations of the extract, more prooxidant property was observed. The study concluded that EEOS anti-cancer activity was as a result of declining cell proliferation, modification

in mitochondrial membrane potential, increasing ROS production and inducing apoptosis in H460 cells.[48] Osteopontin (OPN) is a crucial molecular target in cancer management. In a study, EEOS was used to clarify the anti-metastatic mechanism of OPN in H460 cells; where, EEOS expressively obstructed cell adhesion and cancer progression in H460 cells. EEOS effectively suppressed phosphatidylinositide 3-kinases (PI3K), urokinase plasminogen activator (uPA), EGFR and COX-2 expression levels and declined phosphorylation of Akt in OPN treated H460 cells. Phosphorylation of Akt leads to downstream initiation of the signaling molecules such as mTOR and p70S6K resulting to improved protein synthesis, proliferation and thus, survival. What is more, EEOS meaningfully reduced VEGF production and MMP9 activity in OPN treated H460 cells as well. In particular, Kwak *et al* explained the anti-metastatic mechanism of EEOS, which was declared to be facilitated by inhibition of PI3K/Akt in OPN treated H460 cells.[49] The apoptotic mechanism of EEOS was also investigated in A549 cells by Joseph and Nair; where, EEOS presented activity against A549 cells. EEOS released cytochrome C into cytosol, increased the sub-G1 population, cleaved PARP, and concurrently mounted cas-9 and cas-3 levels. EEOS also increased Bax/Bcl-2 ratio and restrained phosphorylation of Akt and ERK in A549 cells.[50] A recent research conducted on *O. sanctum* for exploring its anti-cancer potential, discovered that EEOS could act as both an anti-proliferative and an apoptotic agent in A549 cells. This study revealed that the active phytoconstituents of *O. sanctum* were chiefly quercetin and eugenol that essentially interacted with the active sites of the αvβ3 integrin, α5β1 integrin, cas-3, cas-9, and VEGF. As observed, hydrogen bonds and Pi-alkyl and Pi-cation interactions were engaged between the phytoconstituents and the active sites. Besides, *in vitro* studies confirmed the anti-proliferative effects of the EEOS against A549 cells.[51] In a study, EEOS significantly inhibited cell adhesion, invasion and MMP9 activity in LLC tumor models, indicating the importance of MMP9 in anti-metastatic character of EEOS. Notably, it was also discovered that EEOS could dose-dependently improve the antioxidative activities of enzymes such as SOD2, catalase and GPx. Taken together, these results supported the exquisite anti-metastatic strength of EEOS.[52]

Origanum compactum

The anti-tumor potency of carvacrol, the main active component of *O. compactum* EO against LC was evidenced by restraining cell growth in A549 cells. EO was also shown to be effective for its anti-mutagenic effects. *O. compactum* EO exhibited strong ability to inhibit urathane-induced mutagenesis.[53] A number of studies have reported the antioxidant activities of *O. compactum* extracts and EO. Recent studies have demonstrated the anti-cancer activity of *O. compactum* as an apoptosis inducer in A549 cells. Apoptosis induction was instructed by activation of caspase signaling which was set off by modulation of Bcl-2 family proteins. Among the EO constituents, thymol was frequently reported to have cytotoxic effects in LC cell lines. The cytotoxicity was as a result of DNA shrinkage and cell cycle arrest in G0/G1 phase. Another known compound from *O. compactum* EO known as carvacrol which is an isomer of thymol, showed a similar activity against LC cell lines.[54] Another study was conducted to explore the anti-proliferative effect of *O. compactum* extract on two human cancer cell lines, A549 and SMMC-7721 hepatoma cells. Contrary to SMMC-7721 cells, treating A549 cells with *O. compactum* extract resulted in a remarkable increase in activation of cas-3 which signaled provocation of the caspase signaling pathway apoptosis.[55]

Salvia miltiorrhiza

Tanshinone (Tan) IIA has been the most studied compound among all the isolates from *S. miltiorrhiza*, thanks to its abundance in the herb. Tans exhibit diverse pharmacological activities, including anti-cancer property.[56] The cytotoxic effects of Tan IIA on several LC cell lines including A549, H460, H146, A-427, H838 and SPC-A1 has been frequently reported.[57,58] Tan IIA halted cell proliferation in LC cell lines in the midst of mitosis in a concentration and time dependent manner mainly via disrupting the mitotic spindle, consequently setting of cells to initiate apoptosis through the mitochondria-mediated apoptotic pathway.[59] Likewise, a further study testified that Tan IIA induced autophagic cell death in H460 cells.[56] NAD(P)H quinone dehydrogenase 1 (NQO1) is an encouraging target in cancer therapy. It was reported that NQO1 might be a potential target of Tan IIA in LC since the anti-cancer effects of Tan IIA were reversed by a specific NQO1 inhibitor treatment.[60] Collectively, the data clearly have shown that Tan IIA have the potential to considerably restrain multiple cancer lines with micromolar IC_{50} levels; comparable with those of acknowledged anti-cancer agents, for instance curcumin, quercetin, and berberine.[61,62] Cryptotanshinone (CPT) isolated from *S. miltiorrhiza* was found to possess cytotoxic and anti-migration effects toward several LC cell lines (SPC-A1, CL1–5, H1299, A-427, H23, and A549). CPT also sensitized cancer cells to a wide extent of anti-cancer drugs such as doxorubicin, etoposide, cisplatin and 5- fluorouracil.[63] Another promising anti-cancer compound, named Tan I, was cytotoxic to a set of LC cell lines (SPC-A1, CL1–5, H1299, H23, A549, CL1–0 and CL1–5) mainly by inducing apoptosis. Tan I was reported to potentially inhibit the proliferation and invasion of CL1–5 cells. Tan I also efficiently inhibited an enzyme named gelatinase in CL1–5 cells *in vitro* and reduced tumor growth and metastasis in CL1–5 tumor

model in SCID mice.[64] Additionally, Tan I restrained interleukin-8, the angiogenic factor involved in cancer metastasis by attenuating the DNA-binding activity of activating protein-1 and NF-κB.[64] In H1299 lung tumor animal model, Tan I (200 mg/kg) increased apoptosis by 193% and decreased tumor growth by 34%, neovascularization by 72% and metastases by 85%.[65] In a transgenic mice model LC, Tan I could appreciably reduce tumor growth by downregulation of Cyclin A, Cyclin B and VEGF protein expressions.[66] Recent literature have shown that dihydrotanshinone (DHT) I isolated from *S. miltiorrhiza* inhibited human LC cell line SPC-A1 cell growth in a concentration and time dependent manner superior than CPT, Tan I and Tan IIA.[56] It was reported that the cytotoxic potential of DHT I might be linked with HIF-1α accumulation reserve.[67] DHT I also induced DNA cleavage in *in vitro* studies via triggering topoisomerase I activity as efficient as camptothecin.[68] A major water-soluble compound isolated from *S. miltiorrhiza*, named danshensu, significantly was reported to improve the radiotherapy prognosis in LLC xenografts in mice. Danshensu improved tumor microcirculation and remodeled tumor vasculature; implying that danshensu might potentially hinder neovascularization.[69] Another study demonstrated that Tan compounds from the methanol extract of *S. miltiorrhiza* roots suppressed the growth of a LC cell line named Glc-82 both *in vivo* and *in vitro* as a result of provoked apoptosis through the mitochondrial-mediated pathway and PTEN-modulated inhibition of PI3K/Akt pathway.[70] Another study has revealed that apart from suppressing lung tumor growth in mice, salvianolate (isolated from *S. miltiorrhiza*) also downregulated expression levels of ATP7A and ATP7B, which are key proteins in cancer progression and chemotherapy of LC. This study attested that salvianolate could considerably decrease the tumor growth of xenograft nude mice[71]; announcing salvianolate as a promising compound for treatment of LC.

Salvia rosmarinus

Rosemary extract (RE) treatment on A549 cells lead to a substantial decline in cell viability with an IC_{50} of 15.9mg/mL. The anti-cancer effects of RE was reported to be similar with resveratrol, a renowned phytochemical with potent anti-cancer properties.[72,73] Colony formation is one of the many strategies of cancer cells in order to survive the destructive impacts of anti-cancer agents or critical environments. Remarkable restriction of colony formation was observed with even as low concentrations as 2.5mg/mL of RE. At 10mg/mL concentration of RE, almost total inhibition of survival was documented. Treating RE resulted in 100% upsurge in cleaved PARP levels in A549 cells, signaling enhanced apoptosis stimulation by RE. Moreover, RE significantly inhibited phosphorylation of Akt and mTOR and total levels of these proteins in A549 cells.[74] All things considered, it has been suggested that RE has of note anti-cancer property and could potentially hold down A549 cancer cells.

Salvia hypargeia

Ulubelen *et al* investigated the cytotoxicity of *S. hypargeia* on different panels of cancer cells. The crude acetone extract obtained from *S. hypargeia* roots was cytotoxically active in all studied cell lines including a LC cell line, LU1. Among 13 isolated compounds, the anti-cancer activity of 8 isolates were investigated; reporting that the two isolates, identified as 6a-hydroxysalvinolone and taxodione, demonstrated more potent cytotoxic activity than others against LU1 cells.[75]

Salvia leriifolia

Tundis *et al* described the isolation and identification of a sesquiterpenoid compound known as buchariol and the flavanone, naringenin from *S. leriifolia* and examined their cytotoxic activity opposed to several human tumor cell lines including a particular NSCLC cell line known as COR-L23 and the A549 cells. The EO isolated from *S. leriifolia* aerial parts displayed a strong inhibitory activity towards COR-L23 cells.[76] The dichloromethane extract was reported to be the most active extract against the studied cell lines with IC_{50} values ranging from 28.1 to 86.2 mg/mL. The anti-cancer activity of the two mentioned isolates, buchariol and naringenin was also studied. Buchariol isolated from the dichloromethane extract presented a significant cytotoxic activity towards A549 cells with an astonishing micromolar level IC_{50} even lower than the positive control, vinblastine (as shown in Table 1).[76] These results may encourage further studies on this sesquiterpene as a lead compound against LC. The ethyl acetate extract also reported to possess a respectable cytotoxic activity against COR-L23 cells. As well, the flavanone naringenin, isolated from the ethyl acetate extract, exhibited interesting cytotoxic effects against COR-L23 cells. Notably, the positive control vinblastine was less potent than naringenin against all the studied tumor cell lines. Sabarinathan *et al* demonstrated that supplementation of laboratory animals with this flavanone modulated the Bcl-2/Bax ratio and upregulated cas-3 and cas-9.[77] In recent years there has been a grown interest in naringenin as a potent anti-cancer flavonoid since numerous reports of its potent cytotoxic activity were documented in the literature.

Salvia prionitis

A diterpenequinone compound named salvicine, obtained from *S. prionitis* by Zhang *et al*, was found to possess potent anti-tumor activity. The reported convincing doses (tumor growth inhibition above 30%) for LAX-83 (human lung adenocarcinoma) and A549 cells were 20 and 30 mg/kg, respectively.[78] The particular cytotoxicity

Table 1. Highly promising results obtained against lung cancer by Tundis et al

Cell line	Extracts				
	Dichloromethane extract	Ethyl acetate extract	Buchariol	Naringenin	Vinblastine
COR-L23	32.9 ± 1.5	20.9 ± 1.4	12.2 ± 0.8	9.1 ± 0.9	45.5 ± 0.7
A549	33.3 ± 1.1	38.9 ± 1.7	3.0 ± 0.04	48.4 ± 2.2	67.3 ± 2.0

The expressed IC_{50} values are in µg/mL.

of salvicine was connected to its apoptosis stimulus nature. Salvicine was reported to exhibit a respected cytotoxic activity on multidrug-resistant (MDR) cancer cell lines by decreasing the expression of multidrug resistance mutation 1 (MDR-1) mRNA in MDR cells. Salvicine behaved as a topoisomerase II exterminator which was further confirmed that its cytotoxic activity was as a result of its ability to stabilize DNA strand breaks and consequently generating anti-cancer effects.[79] Chang *et al* investigated the roots of *S. prionitis* and successfully isolated 6 novel compounds; Among them, prionoid E demonstrated remarkable anti-proliferative activities upon A549 cells.[80]

Salvia yunnanensis

Twelve diterpenoids were isolated from the roots of *S. yunnanensis* by Xia *et al* and all of them were assessed for potential cytotoxicity against several cell lines including H460 cells. 6α-hydroxysugiol, sugiol, and Tan IIA were the three compounds that exhibited slight anti-cancer activities against LC cell lines.[81] A similar study was conducted on *S. yunnanensis* roots, following to isolation of six abietanes, salyunnanin A–F, together with 40 known analogues; moreover, all isolates cytotoxicity against several cancer cell lines were studied. Danshenol A and 6ahydroxysugiol, were reported to demonstrate substantial cytotoxicities upon H460 cells with IC_{50} values of 11.8 and 7.43 µM respectively.[82]

Salvia lachnostachys

Previous studies have reported the isolation of several terpenoids from *S. lachnostachys* including oleanolic acid, ursolic acid and a diterpene known as fruticulin A.[83] Oliveira *et al* evaluated the ethanol extract of *S. lachnostachys* leaves and its fractions for any potential *in vitro* cytotoxic activity against several cancer cell lines including H460. The extract and its fractions illustrated a moderate cytotoxicity against H460 cells. Among fractions, the hexane eluted one was the most potent. Oliveira *et al* successfully isolated two known diterpenes, identified as fruticulin A-B by chromatographic separation; the anti-cancer effects of both of these diterpenes were inspected against several cell lines, reporting fruticulin A as a potential cytotoxic compound with an GI_{50} value of 7.4 µM against H460 cells.[84]

Salvia ballotiflora

In a study, aerial parts of *S. ballotiflora* were phytochemically analyzed by Esquivel *et al* in which they isolated eleven diterpenoids together with an anti-proliferative evaluation against several human cancer cell lines including SK-LU-1. Results of the study revealed that a compound named anastomosine was found to be very toxic to SK-LU-1 cells, 7α-acetoxy-6,7-dihydroicetexone was moderately active against SK-LU-1 and an aromatic diterpenoid named 6,7,11,14-tetrahydro-7-oxo-icetexon proved to be very toxic to the complete panel. Besides, anastomosine and 7α-acetoxy-6,7-dihydroicetexone were identified as the most active molecules in terms of SK-LU-1 cells; nonetheless, the calculated IC_{50} values indicated that 7α-acetoxy-6,7-dihydroicetexone and anastomosine came close to the positive control, adriamycin, in potency.[85] Esquivel *et al* exploration attested that compounds 7α-acetoxy-6,7-dihydroicetexone and anastomosine deserved further studies on their anti-cancer properties. In another comparable research, a hexane-washed chloroform extract of *S. ballotiflora* together with four isolated diterpenoid compounds were tested for their potential cytotoxic activity against three tumor cell lines and A549 cells. The hexane-washed chloroform extract revealed the supreme cytotoxic activity on A549 cells with parallel activity compared to cisplatin.[86]

Ajuga ovalifolia

Liu *et al* investigated cytotoxicity of a new abietane diterpenoid, 3-acetoxylteuvincenone G (3-AG), toward A549 cells reporting a significant rise in the amount of early and late apoptotic A549 cells through activation of downstream cleaved cas-9, accompanied by upregulation of upstream cleaved cas-9, cleaved cas-3, and in due course cleaved PARP. Likewise, administration of 3-AG caused a noticeable upsurge in the level of cas-3. Conclusively, 3-AG induced cas-3-medicated apoptotic pathway in A549 cells. The over-expression of protein tyrosine phosphatase 2 (SHP2) is being observed in numerous mankind tumors; thus inhibition of SHP2 activity brings the growth of tumor cells under control. 3-AG was documented that not only it specifically inhibited SHP2 catalytic activity, but also suppressed phosphorylation of SHP2 and SHP2 expression in A549 cells. In brief, 3-AG restrained A549 cell proliferation whilst inducing cell apoptosis via regulation of SHP2-ERK1/2 and SHP2-AKT pathways.[87] Therefore, 3-AG might be considered as an inexperienced optimistic SHP2 inhibitor for treatment of NSCLC. Further studies conducted on *A. ovalifolia* indicated that another isolated abietane diterpenoid,

Ajuforrestin A, exhibited direct inhibitive activity on SHP2 catalytic domain. Treating A549 cells with Ajuforrestin A significantly restrained cancer cells proliferation as the occasion of cell apoptosis via inhibiting the SHP2–ERK/Akt pathways.[88]

Isodon silvatica

As far as we know, *Isodon* spp. are rich in diterpenoid compounds that are renowned for showing anti-tumor bioactivity.[89] In a study on *I. silvatica*, acetyl-macrocalin B (A-macB) was isolated from the plant extract, where its cytotoxic activity against NSCLC were evaluated underlying its mechanisms of action. A-macB successfully restrained H1299 and A549 cells proliferation, generated apoptosis and stalled cells in the G2/M phase. The related mechanisms were incitement of ROS production and activating the p38 mitogen-activated protein kinase (MAPK)-mediated, cas-9-dependent pathway of apoptosis. NAC and a certain p38 inhibitor agent named SB203580 could efficiently incapacitate A-macB, consequently arresting apoptosis. A-macB induced G2/M phase arrest by activating the checkpoint kinase (CHK) 1/2-Cdc25C-Cdc2/cyclin B1 axis. Furthermore, A-macB admirably inhibited tumor growth in a mouse xenograft model deprived of evident toxicity for normal tissues.[90] According to the obtained data in terms of efficacy and safety, we might propose A-macB as a prospective lead agent for additional investigations on anti-cancer drugs.

Lavandula dentata

The reported bioactivities of *L. dentata* EO were claimed to be due to the presence of monoterpenes mainly linalyl acetate and linalool.[91] The EO was documented to possess cytotoxic properties. Justus *et al* conducted a study on *L. dentata* EO in its both gas and fluid phases to investigate its cytotoxic effects on a NSCLC cell line Calu-3 cells, and reported further observations of its anti-cancer properties. Promising results were obtained; *L. dentata* EO treatment resulted in a substantial decline of Calu-3 cells viability and as reported, up to 84% of growth inhibition was witnessed in a time-dependent manner. Both necrosis and apoptosis rates were remarkably raised in Calu-3 cancer cells upon treatment of lavender EO in its gas phase.[92]

Plectranthus amboinicus

Previous studies on *P. amboinicus* stem extract revealed that the plant contains high quantities of phenols, proanthocyanidins and flavonoid compounds such as RA, gallic acid, caffeic acid, rutin and quercetin. These polyphenol compounds have been reported to link up with the antioxidant and anti-tumor properties.[93] A study was conducted on *P. amboinicus* methanol extracts to determine its anti-proliferative effects on A549 cells; reporting the extract to possess moderate anti-cancer activity on the studied LC cell line.[94] Elsewhere, the anti-cancer activity of *P. amboinicus* EO on lung metastasis was evaluated; reporting the EO to possess a considerable cytotoxic activity on a highly metastatic (mostly invade towards lungs) melanoma cell line named B16F-10. A major reduction of tumor development in lungs was reported in mice upon the EO treatment as an indicator of *P. amboinicus* EO anti-lung metastatic effect. Plus, the EO refined lung cells microenvironment. Carvacrol and thymol were frequently reported for their potential anti-cancer properties in different studies and were both reported to be broadly present in *P. amboinicus* EO.[95] Novel cancer therapies emphasize the anti-angiogenic property as an exceedingly appreciated strategy in treatment of cancer. It was reported that *P. amboinicus* EO efficiently prohibited neovascularization in tumor environment which is assumed to be due to the presence of thymol and carvacrol.[96]

Pogostemon auricularius

Three terpenoids known as pogostemins A-C were isolated from *P. auricularius* by a study conducted by Nguyen *et al*; cytotoxicity of these isolates was assessed against a panel of cancer cell lines including SK-LU-1. It has been reported that these meroterpenoids indicate signs of cytotoxicity as opposed to all studied cancer cell lines.[97] To explain the related anti-cancer mechanism of pogostemin A and how it provoked apoptosis in SK-LU-1 cells, the effects of pogostemin A on cas-3 were investigated. It was proven that cas-3 activity increased significantly upon pogostemin A treatment.[98]

Perilla frutescens

Wanisa *et al* conducted a study to explore the antioxidant effects of *P. frutescens* leaves extract (PLE) and investigate its anti-inflammatory effects on TNF-α- treated A549 cells. PLE was reported to demonstrate a significant anti-inflammatory effect in aroused A549 cells mainly via prevention of ROS formation and by decreasing expressions of TNF-α, IL-1β, IL-8 and COX-2.[99] PMFF is one of the environmental pollutants which mainly spread in the air as a result of forest fires. It is reported to induce inflammation, oxidative stress and metastasis in cancer cells due to the presence of polycyclic aromatic hydrocarbons. Perilla seeds contain a considerable amount of polyphenols, such as RA. Pintha *et al* investigated the antioxidative and anti-metastasis activities of RA rich fractions (RA-RF) isolated from perilla seeds and the principal mechanisms involved, in pre-exposed A549 cells to PMFF. It was reported that PMFF significantly triggered invasion, migration, ROS production, MMP9 activity, expression of inflammatory cytokines, Akt phosphorylation and lastly overexpression of c-Jun and p-65-NF-κB in malignant cells; events that all were suppressed by RA-RF. Plus, RA-RF reduced COX-2, IL-6, IL-8 and TNF-α expressions as well. Conclusively, RA-

RF was described to exhibit its anti-metastasis properties via c-Jun, p-65-NF-κB, and Akt signaling pathways.[100] RA-RF was suggested to be introduced and utilized as an inhalation drug for prevention of lung inflammation and LC metastasis. El-Hafeez *et al* studied a modified isolated compound named 8-hydroxy-5,7-dimethoxyflavanone from PLE which showed inhibitive activity on A549 cells. They documented that this isolated methoxyflavanone (PDMF) was able to notably inhibit cell proliferation of LC cell line A549 cells via induction of apoptosis through cell cycle arrest at G2/M phase. The PDMF could successfully increase the levels of anti-tumor agent p53 and its expression in cancer cells. PDMF also raised upregulation of apoptotic caspases, cas-9 and cas-3. These results supported that PDMF resembled to a functional LC-preventive plant-derived agent that triggered apoptosis through cell cycle arrest.[101] El-Hafeez *et al* further studies on *P. frutescens* anti-cancer activity also revealed that PDMF could synergize with TKI agents and intensify their anti-tumor strength on A549 cells. The synergistic anti-tumor effect was fulfilled by induction of cell cycle arrest at both G2/M and G1 phases.[102] The effects of PLE on two cancer cell lines, namely, HCT116 and H1299 (a colorectal cancer cell line and a LC cell line, respectively) were investigated. Treatment of these cells with PLE, dose-dependently inhibited cancer cells proliferation by 52-92% and completely abolished the colony formation in soft agar. Treatment with 350 µg/mL concentration of PLE resulted in multiplied population of sub-G1 cells in both studied cell lines, confirming its apoptosis-inducing character. Moreover, PLE effectively inhibited H1299 cells migration rate up to 58% and decreased both cell lines extracellular adhesion by 25-46%. Conclusively, PLE was introduced as a potential anti-cancer agent against LC.[103] Several other studies were performed on *P. frutescens* to probe its anti-cancer potency and confidently all of them reported a notable anti-cancer activity but only a few were described here.

Mentha piperita

The anti-cancer effects of *M. piperita* leaves EO was investigated upon several cancer cell lines and as it was reported, the EO was significantly active against SPC-A1 cells with a reported IC_{50} value of 10.89 mg/mL.[104] Yücel *et al* explored the *in vitro* anti-proliferative effects of *M. piperita* EO in A549 cells; where, it was found to effectively decrease the viability of NSCLC cells with respectable low IC_{50} values. As reported, peppermint EO also changed the morphology of A549 cells, resulting to changes that might be interpreted as a pro-apoptosis state.[1]

Mentha pulegium

Farnam *et al* inspected the ethanol extract of *M. pulegium* aerial parts and its anti-cancer effects on two different cell lines; an invasive breast cancer cell line named MCF7 and the renowned A549 cells representing for LC. The ethanol extract exhibited degrees of cytotoxicity on both of these cell lines in a dose-dependent manner. For A549 cells, IC_{50} was reported about 49 µg/mL; as reported, the MCF7 cells proliferation was halted at G2/M phase; conversely, the A549 cells detained in G0 phase of the cell cycle after treating with *M. pulegium* extract.[105]

Four other *Mentha* spp.

In an *in vitro* study, Sharma *et al* evaluated the anti-cancer potential of several Mentha spp. namely, *M. arvensis*, *M. longifolia*, *M. spicata* and *M. viridis* versus multiple cancer cell lines including a bronchioalveolar carcinoma cell line, known as NCI-H322 and A549 cells. Methanol extracts of these Mentha spp. were reported to show promising signs of cytotoxic effects (up to 70-97% of growth inhibition) upon NCI-H322 cells; notably, all methanol extracts of these Mentha species were more potent than the positive control paclitaxel against NCI-H322 cells.[106]

Polygonum cuspidatum

Cachexia, one of the most frequent risk factors for increased mortality of cancer, is briefly characterized as degeneration of body fat and muscles. The effects of emodin – a highly abundant compound in *P. cuspidatum* extracts – on cancer-induced cachexia, were explored in an *in vivo* study by Fang *et al* using A549 tumor-bearing mice. Emodin-contained extracts were reported to significantly reduce cachexia symptoms in lung tumor models.[107] Elsewhere, *P. cuspidatum* roots extracts were investigated in case of possessing cytotoxic activity on human LC cells. It was reported that the extracts inhibited both H1650 and A549 cells proliferations by inducing apoptosis, suggesting *P. cuspidatum* as a cytotoxic plant against LC.[108] Resveratrol, a phytoalexine compound abundantly found in *P. cuspidatum*, was reported to appreciably downgrade tumor volume, tumor weight and metastasis (56%) in LLC tumor model mice at promising doses ranging from 2.5 to 10 mg/kg. Resveratrol successfully hindered DNA synthesis in LLC tumor cells with an IC_{50} value of 6.8mmol/L. Moreover, at concentrations of 10–100mmol/L, resveratrol was reported to appreciably inhibit formation of capillary-like tubes in an *in vivo* study; introducing it as a potential anti-angiogenic substance. Elsewhere, besides confirming the anti-tumor and anti-metastatic effects of resveratrol, it was supposed that inhibition of DNA synthesis could be the key mechanism for its anti-cancer effects.[109]

Vitex negundo

Xin *et al* investigated the cytotoxic activity of a lignan comprised blend isolated from *V. negundo*, on a variety of cancer cell lines including A549 cells**.** The observed IC_{50} for the A549 cells was a respected value of 10.84 µg/mL. Lignans extracted from *V. negundo* were reported to

exhibit their cytotoxic activity through restraining LC cells at G2/M cell cycle phase and apoptosis provocation.[110]

Nepeta cataria

Fan *et al* investigated the effect of total flavonoids isolated from *N. cataria* (TFS) on A549 cells and reported its anti-tumor effect on A549 cells. Both necrosis and apoptosis rates of the studied cells were meaningfully superior to those in the control group and this effect was in a concentration and time dependent manner. It was reported that TFS meet its anti-cancer effects through regulating the PI3K-Akt signaling pathway and by interrupting the expression of microRNA-126[111]; suggesting that the merit flavonoids of *N. cataria* might be used as a novel therapeutic agent for treating LC.

Thymus spp.

Oliviero *et al* probed the anti-inflammatory and cytotoxic activity of hydroalcohol extracts of *T. vulgaris* in H460 cells and paralleled the results with those obtained from normal tracheal and bronchial cells. Interestingly, the selective cytotoxic effect of the extract on H460 cells in comparison to normal cells was documented. The reported capability of the extract in modulating the cytokines IL-1β and IL-8 and interacting in NF-κB p65 and NF-κB p52 pathways - that all led to prevention of angiogenesis, tumor progress and metastasis - were magnificent.[112] Elsewhere, the anti-cancer activity of three thymus species EO on multiple cell lines including H460 (representing for LC) was investigated; where, thymol was reported to be the chief component in all studied EOs. The isolated thymol exhibited the most activity against H460 cells with an IC_{50} value of 37.17μg/mL.[113] Elsewhere, Zu *et al* investigated the cytotoxic effects of 10 plants EOs on cancer cell lines including A549 cells. The thyme EO selectively displayed the highest anti-proliferative activity against A549 cells among all studied EOs with an IC_{50} value of 0.011%v/v.[114]

Anisomeles indica

Basappa *et al* phytochemically investigated *A. indica* leaves EO and surveyed its biological properties. The anti-cancer activity was analyzed by assessing cytotoxic effects on cancer cells in four cancer cell lines including A549, on behalf of LC. Admirably, inhibition of cell proliferation in all investigated cell lines was endorsed. A549 cells growth inhibition was achieved with IC_{50} value of 63.36 μg/mL.[115] Ovatodiolide isolated from *A. indica,* was reported to trigger DNA damage followed by increased ROS production. Moreover, ovatodiolide treatment could inhibit cell proliferation in both H1299 and A549 cells by inducing apoptosis with outstanding IC_{50} values of 10 and 4μM after 48h of treatment. There are some identified proteins categorized as DNA damage-related molecules, such as ATM, ATR and CHK1/CHK2, that their expressions raise following DNA damage. It was reported that levels of these proteins upraise after ovatodiolide treatments in cancer cells. Furthermore, ovatodiolide efficiently prompted apoptosis via both extrinsic and intrinsic pathways; succinctly said, raising p53, Bax, and death receptor 5 protein levels, decreasing Bcl-2 and Myeloid cell leukemia-1 (Mcl-1) expressions, and activating cas-3, cas-8 and cas-9 were the associated anti-cancer mechanisms.[116]

Monarda citriodora

Thymol was reported to be the major (82%) component of *M. citriodora* EO (MCEO). The cytotoxic potential of MCEO in a leukemia cancer cell line known as HL-60 cells was documented. The reported mechanisms of action were through apoptosis and disruption of the PI3K/Akt/mTOR signaling cascade. Both MCEO and thymol inhibited the PI3K/Akt/mTOR signaling pathway and MCEO activity was reported to be significantly higher. Both MCEO and thymol, inhibited cell proliferation in A549 cells, as well. The reported mechanism of action for this cytotoxic effect was inducing apoptosis through both intrinsic and extrinsic pathways that were further confirmed by increased expression levels of death receptors (such as TNF-R1, Fas and cas-9) and subsiding the Bcl-2/Bax ratio.[117]

Teucrium polium

Haïdara *et al* investigated aqueous extract of *T. polium* for its cytotoxic activity against NCI-H322 and A549 cells. The extract inhibited cell growth, deregulated cell cycle and induced a significant apoptosis rate in the studied LC cell lines. Bearing in mind that flavonoid compounds have a well-established anti-cancer property, it was proposed that the obtained results could be related to p53 protein and other regulators of cell death.[118]

Table 2 briefly depicts the obtained IC_{50} values or other potency indicators of the studied Lamiaceae plants with potential activity against LC. A succinct summary of all studied papers, including the studied compound(s), study results, and possible anti-cancer mechanism(s) of action are provided in Table 3.

Concluding remarks

Among all the studied medicinal plants of Lamiaceae, effective in LC, 31 plants were chosen for this review considering their potency and efficacy. Different spp. of *Salvia, Thymus, Scutellaria, Ocimum* and *Mentha* were reported to exhibit promising activities against LC both in *in vitro* and *in vivo* studies. So long as possible, the mechanisms of action for the corresponding anti-cancer effects were described as well. It was witnessed that Lamiaceae plants affect LC by several different noteworthy mechanisms; such as, apoptosis induction in cancer cells through triggering both intrinsic and extrinsic

Table 2. Reported IC_{50s} or other potency indicators against LC cell lines from the plants of Lamiaceae

Studied plant	Studied compound(s)	Studied cell line(s)	Reported IC_{50} or other potency indicator	References
Ajuga ovalifolia	3-Acetoxylteuvincenone G	A549	IC_{50} = 10.70 ± 0.14 µM	87
	Ajuforrestin A	A549	IC_{50} = 8.68 ± 0.96 µM	88
Anisomeles indica	Leaves EO	A549	IC_{50} = 63.36 µg/mL	115,116
	Ovatodiolide	H1299, A549	IC_{50} = 10 and 4 µM, respectively after 48h of treatment	
four other *Mentha* spp.	Methanol extract of whole plants	NCI-H322	with a concentration of 100 µg/mL, all four spp. inhibited cell growth near 71-85%	106
Isodon silvatica	Acetyl-macrocalin B	H1299, A549	IC_{50} = 0.61 µM and 2.20 µM, respectively after 72 h treatment	90
Lavandula dentata	EO	Calu-3	IC_{50} = 388.84 µg/mL, after 72 h of treatment	92
Melissa officinalis	EO	A549	with a concentration of 100 µg/mL, resulted in > 80% growth inhibition after 72 h of treatment	35
		A549	77.8% growth inhibition with outstanding IC_{50} value below 5 µg/mL	42
Mentha piperita	leaves EO	SPC-A1	IC_{50} = 10.89 mg/mL	104
		A549	IC_{50} = 2.12% for 24 h	1
Mentha pulegium	ethanol extract	A549	IC_{50} = 49 µg/mL	105
Monarda citriodora	EO	HL-60	IC_{50} = 22 µg/mL	117
Nepeta cataria	extracted total flavonoid	A549	proliferation inhibition of about 57.41% after 36 h treatment	111
Ocimum gratissimum	aqueous extract	A549	The viability was significantly decreased to near 27.5% of control with 800 µg/mL concentration	43
	oleanolic acid		ED_{50} = 3.16 µg/mL	44
Ocimum sanctum	ethanol extract	A549	100 µg/mL induced the most severe cytotoxicity	47
		NCI-H460	150 µg/mL exhibited maximum decline in cell viability	48
Origanum compactum	ethyl acetate extract	A549	IC_{50} = 198 ± 12 µg/mL	55
Perilla frutescens	PDMF	A549	IC_{50} = 53.5 µg/mL	101
	ethanol extract of leaves	HCT116	IC_{50} = 76 µg/mL after 72 h treatment	103
Phlomis younghusbandii	phlomisoside F	A549	IC_{50} = 54.51 µM	10
Plectranthus amboinicus	methanol extract	A549	IC_{50} = 872.75 ppm	94
Pogostemon auricularius	pogostemin A	SK-LU-1	IC_{50} = 12.76 ± 0.88 µg/mL	98
Polygonum cuspidatum	resveratrol	LLC tumor cells	IC_{50} = 6.8 mmol/L	109
	ethanol extract	H1650	IC_{50} = less than 0.2 mg/mL	108
Salvia ballotiflora	7α-acetoxy-6,7-dihydroicetexone	SK-LU-1	IC_{50} = 0.46 ± 0.05 µM	85
	hexane-washed chloroform extract	A549	IC_{50} = 2.29 µg/mL	86
Salvia hypargeia	6- hydroxysalvinolone	LU1	ED_{50} = 4.2 µg/mL	75
Salvia lachnostachys	fruticulin A	H460	GI_{50} = 7.4 µM	84
Salvia leriifolia	naringenin	COR-L23	IC_{50} = 9.1 ± 0.9 µg/mL	76
	buchariol	A549	IC_{50} = 3.0 ± 0.04 µg/mL	
Salvia miltiorrhiza	Tan IIA	A549	IC_{50} = 5.32 mM	60
	Tan I	in a H1299 lung tumor animal model	with a concentration of 200 mg/kg, increased apoptosis by 193% and decreased tumor growth by 34%, neovascularization by 72% and metastases by 85%	65
	DHT I	SPC-A1	IC_{50} = 1.36 µg/mL, after 72h treatment	56
	salvianolate	lung carcinoma xenograft with A549 cells	a concentration of 50 mg/kg conferred the highest tumor growth inhibition rate	71
Salvia prionitis	salvicine	LAX-83, A549	tumor growth inhibitions (above 30%) were 20 and 30 mg/kg, respectively	78
	prionoid E	A549	IC_{50} = 0.72 µM	80

Table 2. Continued.

Studied plant	Studied compound(s)	Studied cell line(s)	Reported IC_{50} or other potency indicator	References
Salvia rosmarinus	Rosemary extract	A549	IC_{50} = 15.9mg/mL	72, 73
Salvia yunnanensis	6α-hydroxysugiol	NCI-H460	IC_{50} = 7.4 µM	81
Scutellaria baicalensis	baicalein, baicalin, wogonin and wogonoside	A549	Optimal doses in xenograft mice model were reported to be 40, 80-100, 60-100, and 80 mg/kg, respectively	18
	roots ethanol extract, baicalin, baicalein and wogonin	A549	IC_{50} = 102.1 ± 4.8, 28.6 ± 2.3, 21.5 ± 1.5 and 11.0 ± 2.7 µg/mL	19
Scutellaria barbata	ethanol extracts	A549	IC_{50} = 0.21 mg/mL	28
			IC_{50} = 0.5 mg/mL	30
	isolated polysaccharides	95-D	IC_{50} = 35.2 µg/mL	31
Teucrium polium	aqueous extract	H322, A549	treatment with 100, 150 and 200 µl/mL of extract led to a dose-dependent increase in cell death	118
Thymus spp.	thymol	H460	IC_{50} = 37.17 µg/mL	113
	thyme EO	A549	IC_{50} = 0.011%v/v	114
Vitex negundo	a lignan comprised blend	A549	IC_{50} = 10.84 µg/mL	110

Table 3. Promising plants from Lamiaceae as leads against lung cancer (a brief summary)

Plant name	Studied compound(s)	Results	Proposed mechanism	References
Ajuga ovalifolia	ajuforrestin A	significantly restrained A549 cells development	• interfering with of SHP2–ERK/Akt pathways	87,88
	3-acetoxylteuvincenone G	noteworthy rise in A549 cells apoptosis	• suppressed SHP2 phosphatase activity • regulation of SHP2-ERK1/2 and SHP2-Akt pathways	
Anisomeles indica	ovatodiolide	concurrently triggered apoptosis and hindered cell proliferation in A549 and H1299 cells	• both intrinsic and extrinsic pathways were involved established by the increasing p53, Bax, and death receptor 5 proteins, decreasing Mcl-1 and Bcl-2, and activation of cas-3, -9 and -8 • activated ATM/ATR and CHK1/CHK2 • G2/M cell cycle arrest by sabotaging in multiple proteins expressions at a mRNA level • provoked ROS generation	115,116
	essential oils of leaves	inhibited proliferation of all four cell lines including A549 cells	-	
four Mentha spp.	methanol extracts	anti-proliferative potency was more than the positive control Paclitaxel against NCI-H322 cells	-	106
Isodon silvatica	acetyl-macrocalin B	successfully decreased H1299 and A549 cells viability and proficiently suppressed tumor size growth	• induced cellular ROS generation, triggered the p38 MAPK signaling pathway • initiated the cas-9-dependent apoptosis cascade • triggered apoptosis and delayed cells in the G2/M phase	90
Lavandula Dentata	essential oil	significant reduction of cell viability	• apoptosis and necrosis	91,92
Melissa officinalis	aqueous extract	anti-proliferative effects in A549 cells	• concurrent suppression of hTERT and VEGF-A	33-37,39,41,42
	ethanol extract	induced apoptosis in H460 cells and affected their cell cycle; even at the lowest concentrations, significantly reduced viability of the A549 cells	• upregulated p53 protein expression	
	essential oil	geraniol inhibited the viability of several cancer cell lines	• chiefly via exerting its antioxidant action	
Mentha piperita	essential oils from leaves	significantly active against SPC-A1 cell; principal morphology changes in A549 cells	-	104

Table 3. Continued.

Plant name	Studied compound(s)	Results	Proposed mechanism	References
Mentha pulegium	ethanol extract of the aerial parts	degrees of cytotoxicity on both A549 and MCF7 cells	• accumulation of A549 cells in G0 resting phase	105
Monarda citriodora	essential oils and thymol	inhibited cell growth in multiple cancer cell lines including A549 cells	• provoked apoptosis via increased expression of Bcl-extra-large, cas-3, cas-8, cas-9 and cleavage of PARP-1 • apoptosis was triggered by both intrinsic and extrinsic pathways that were established by improved expressions of Fas, TNF-R1, cas-9, loss of mitochondrial membrane potential and falling of Bcl-2/ Bax ratio • inhibited the PI3K/Akt/mTOR signaling pathway	117
Nepeta cataria	flavonoids	exhibited a significant anti-tumor effect against A549 cells	• disturbed microRNA-126 expressions and regulated the PI3K-Akt pathway	111
Ocimum gratissimum	aqueous extract	dose-dependently, decreased the viability of A549 cells	• intensified protein level of Apaf-1 and Bak • improved activation of cas-3, cas-9 and cas-8 and phosphorylation of JNK and p38 MAP kinase • lessened the level of Bcl-2 • inhibited the phosphorylation of ERK	43-45
	oleanolic acid	showed bioactivity against all studied solid tumor cell lines	-	
Ocimum sanctum	ethanol extract	decreased A549 cells viability	• up-regulation of ROS and cas-3 expression • decreased Bcl-2	46-52
		the higher concentration of the extract, the more prooxidant property in H460 cells	• decreased cell proliferation • increased ROS production modulation of the mitochondrial membrane potential	
		notably restrained cell adhesion and invasion of H460 cells	• reducing PI3K expression and Akt phosphorylation	
		cytotoxic activity upon A549 cells; increased sub-G1 cell group and increased apoptosis-related proteins in A549 cells	• cleaved PARP • released cytochrome C into cytosol • triggered cas-9 and -3 • raised the ratio of Bax/Bcl-2 hindered the phosphorylation of ERK and Akt	
		drastically inhibited cell adhesion and invasion of LLC tumor models	• inactivation of MMP9 boosting antioxidant activity by intensifying SOD2, catalase and GPx enzymes	
Origanum compactum	essential oil	inhibited cell growth in A549 cells	• capacity of carvacrol to prevent lipid oxidation	53-55
	extracts	the greatest antioxidant activity was obtained from the aqueous extract	-	
	ethyl acetate extract	cytotoxic effect on A549 cells	• initiation of caspase signaling via alterations in Bcl-2	
Perilla frutescens	ethanol extract of leaves	antioxidant activity but with no cytotoxicity against TNF-α- treated A549 cell line	• reduction of ROS, IL-8, IL-1β, COX-2 and TNF-α • suppressed MMP9 activity • p-65-NF-κB, c-Jun and Akt signaling pathways	99-103
	rosmarinic acid rich fractions of seeds	anti-inflammatory, antioxidant and anti-metastasis impressions in A549 cells		
	8-hydroxy-5,7-dimethoxyflavanone from leaves	carcinostatic activity on A549 cells; synergized with anti-cancer TKI agents to amplify tumor suppressive potency on A549 cells	• triggered p53-mediated G2/M cell cycle arrest synergistic anti-tumor effects were justified by provocation of cycle arrest at both G1 and G2/M phases	
	ethanol extract of leaves	inhibited cell adhesion, proliferation and migration of H1299 and HCT116 cells	• significantly increased sub-G1 cell population	

Table 3. Continued.

Plant name	Studied compound(s)	Results	Proposed mechanism	References
Phlomis younghusbandii	phlomisoside F	reduced the proliferation, migration and invasion of A549 cells	• activated the intrinsic mitochondrion-mediated apoptosis pathway by down-regulating the expression of Bcl-2 and upregulating the expression of cas-3, cas-9 and Bax • decreased COX-2 expression	8-10
Plectranthus amboinicus	methanol extracts of the stem	extracts possess cancer cell specific cytotoxic activity against A549 cells	-	94,96
	essential oil	noteworthy cytotoxicity on B16F-10 cells; significant inhibition of tumor nodule formation; anti-lung metastatic and anti-angiogenic effects		
Pogostemon auricularius	pogostemonons A-C isolated from methanol extract	modest inhibitory effect upon the studied human cancer cell lines	-	97,98
	pogostemin A isolated from methanol extract	apoptosis inducing effects were reported	• enhanced cas-3 movements	
Polygonum cuspidatum	emodin isolated from hydro-alcohol extract	emodin-containing extracts significantly alleviated skeletal muscle atrophy in A549 tumor-bearing mice	• downregulated fat browning-related genes	107-109
	ethyl acetate and ethanol extracts of roots	induced apoptosis in A549 and H1650 cells	-	
	resveratrol	reduced tumor size and metastasis in mice LLC tumor models	• inhibition of angiogenesis and DNA synthesis	
Salvia ballotiflora	dichloromethane extract of aerial parts and its compounds	Anastomosine and 7α-acetoxy-6,7-dihydroicetexone were the most active isolated compounds against SK-LU-1 cells	-	85,86
	chloroform extract of aerial parts	hexane-washed chloroform extract had the topmost cytotoxic effect on A549 cells		
Salvia hypargeia	acetone extract	cytotoxically active in all studied cell lines including LU1 cells; cytotoxicity of 8 isolated compounds from *S. hypargeia* roots were proved	-	75
Salvia lachnostachys	leaves extract	proliferation of different cancer cell lines were affected	-	84
Salvia leriifolia	hexane extract	remarkable results against COR-L23 tumor cell lines	-	76
	essential oil	strong inhibitory activity was observed towards COR-L23		
	buchariol isolated from the dichloromethane extract	cytotoxic activity towards A549 cells		
	naringenin isolated from the ethyl acetate extract	interesting cytotoxic effects against the COR-L23 tumor cells	• modulation of Bcl-2/Bax ratio upregulation of cas-3 and -9	
Salvia miltiorrhiza	tanshinone IIA	restrained the proliferation of several LC cell lines	• induced ROS production • NQO1 might be a potential target	56,69-71
	cryptotanshinone	sensitized various tumor cells to multiple anti-cancer agents for instance etoposide and TNF-α	• induction of apoptosis via G0/G1 cell cycle arrest by interrupting PI3K/PKB/GSK3b pathway	
	Tan I	induced a significant amount of apoptosis and anti-migration effects in LC tumor model cells; considerably reduced lung tumor growth	• suppressed IL-8 activity via modulating NF-κB hindered protein expression of cyclin A/B and VEGF	
	DHT I	more potent than Tan IIA, Tan I and CPT in inhibition of SPC-A1 cells growth	• reducing HIF-1α accumulation induced DNA cleavage via affecting topoisomerase I	
	salvianolate	significantly decreased tumor size in cancer mice models	• downregulation of ATP7B and ATP7A expression levels	
	methanol extract	suppressed the growth of Glc-82 cells both *in vitro* and *in vivo*	• induced apoptosis via mitochondrial pathway of apoptosis and PTEN-mediated inhibition of PI3K/Akt pathway	

Table 3. Continued.

Plant name	Studied compound(s)	Results	Proposed mechanism	References
Salvia prionitis	salvicine	potent activity against all four experimental animal model	-	78-80
		major cytotoxic activity upon malignant tumor cells both in *in vivo* and *in vitro* studies	• down-regulation of MDR-1 expression • disrupted topoisomerase II	
	3-keto-4-hydroxysaprorthoquinone	cytotoxic effects on HL-60 cells	-	
	prionoids E	significant cytotoxicity upon A549 cells		
Salvia rosmarinus	extracts	negative growth effect on A549 cells even at low doses; enhanced apoptosis of A549 cells	• increased cleaved PARP • significantly inhibited Akt phosphorylation	74
		exerted direct cytocydal effects	• up-regulation of nitric oxide (NO) in cancer cells	
Salvia yunnanensis	acetone extract	almost all of the isolated compounds exhibited a moderate to high cytotoxic effect on several human cancer cell lines including H460	-	81,82
Scutellaria baicalensis	baicalein, baicalin and wogonin	highly cytotoxic against SK-LU-1 and A549 cell lines	• upregulated expressions of p53 and Bax • downregulated expressions of cyclinA, Id1 protein, N-cadherin, vimentin , VEGF-A and FGFR2	18-20,22-27
	crude ethanol extracts	selectively cytotoxic to A549 and SK-LU-1 cells; reduced proliferation and provoked apoptosis in EGFR TKI-resistant NSCLC cells	• suppression of proliferation, cell-cycle arrest, blockade of invasion and metastasis suppressed STAT3 activity	
	aqueous extract of roots	decreased proliferation and invasion of A549 cells and arrested the cell cycle at S phase	• induced apoptosis by increasing cas-3, PARP cleavage, and AMPK and reducing mTOR	
Scutellaria barbata	ethanol extracts	greatly inhibited A549 cell growth; remarkable cytotoxic effects of SB on four LC cell lines; inhibited angiogenesis in tumor microenvironment	• regulated several apoptotic pathways, including EGFR inhibition and/or p53 activation • inhibited HIF-1α expression	28-32
	baicalein, wogonin and scutellarin	might be effective in treatment of NSCLC	• aimed for iNOS, Bax, and P38 • anti-inflammatory and anti-angiogenesis activity • promoting apoptosis regulated the vital proteins interrelating NSCLC including NF-κB, COX-2, ERK, Bax and CDK1	
	isolated polysaccharides	anti-cancer effects on 95-D cells both *in vitro* and *in vivo*	• directly regulated the c-Met signaling pathway	
Teucrium polium	aqueous extract	inhibited cell development and induced significant rates of apoptosis in NCI-H322 and A549 cells	• might be related to p53 and other regulators of apoptosis	118
Thymus spp.	standardized hydroalcohol extract	discriminating cytotoxic effects on H460 cells	• restricted the cytokines IL-1β, IL-8 and NF-κB p52/65 pathways	112-114
	essential oils of three thymus species	*T. serpyllum* EO exhibited the topmost activity against the LC cell line	-	
	essential oils of 10 plants	out of 10 studied plants, thyme EO exhibited the highest activity against the A549 cells	-	
Vitex negundo	a mixture of lignan compounds	respectable cytotoxic activity on a panel of cancer cell lines including A549	• apoptosis induction through G2/M phase cell cycle arrest	110

mitochondrion-mediated apoptosis pathways, disrupting cell-cycle and suppression of cancer cell proliferation by aiming at multiple targets, regulate mRNA expression of some key apoptosis modulator proteins, blockade of invasion and metastasis by different mechanisms, for instance, with downregulation of VEGF-A, HIF-1α and hTERT secretions, as well as overcoming drug resistance for some cancer chemotherapeutic agents like TKIs. Although several plant extracts or pure isolated compounds are astoundingly potent against LC cell lines or tumor models, many of these invaluable elements are overlooked, and the studies remain incomplete,

Research Highlights

What is the current knowledge?

- Lung cancer is the leading cause of cancer associated deaths worldwide.
- Current therapeutic guidelines for cancer consist of multiple plant-derived chemotherapeutic agents.
- Several plants of Lamiaceae have shown remarkable anti-cancer activities in different studies.
- Despite the recent efforts to cure lung cancer, survival rates of patients are rather disappointing.

What is new here?

- All the remarkable plants of Lamiaceae with proven activity against lung cancer are brought together.
- Different anti-cancer mechanisms of action versus lung cancer are collectively described.
- Several promising agents for treating lung cancer have been introduced in view of cytotoxic studies.

necessitating more effort for further investigations, delving deeper into the molecular mechanisms of how these phytochemicals inhibit lung cancer would be valuable, revealing specific signaling pathways or targets could guide future drug development. As regards, future research could be focused on both preclinical studies upon the potent phytochemicals and also on the toxic dosage of them to strengthen the evidence base knowledge. It is expected that this report would help scientists with having a better, concise attitude towards detailed evaluation of Lamiaceae plants' potential for LC treatment.

Competing Interests

The authors declare no conflict of interest neither with a person nor an institute.

Ethical Statement

The whole study was registered at Tabriz University of Medical Sciences.

Authors' Contribution

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Project administration: Sanaz Hamedeyazdan.
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References

1. Yücel D, Sezer CV, Yücel E, Kutlu HM. Antiproliferative and cytotoxic activities of *Mentha x piperita* L. essential oil in non-small cell lung cancer cells. *Indian J Exp Biol* **2022**; 60: 753-8. doi: 10.56042/ijeb.v60i10.47280.
2. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. *Contemp Oncol (Pozn)* 2021; 25: 45-52. doi: 10.5114/wo.2021.103829.
3. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin* **2023**; 73: 17-48. doi: 10.3322/caac.21763.
4. Sitarek P, Merecz-Sadowska A, Śliwiński T, Zajdel R, Kowalczyk T. An in vitro evaluation of the molecular mechanisms of action of medical plants from the Lamiaceae family as effective sources of active compounds against human cancer cell lines. *Cancers (Basel)* **2020**; 12: 2957. doi: 10.3390/cancers12102957.
5. Greenwell M, Rahman PK. Medicinal plants: their use in anticancer treatment. *Int J Pharm Sci Res* **2015**; 6: 4103-12. doi: 10.13040/ijpsr.0975-8232.6(10).4103-12.
6. Ijaz S, Akhtar N, Khan MS, Hameed A, Irfan M, Arshad MA, et al. Plant derived anticancer agents: a green approach towards skin cancers. *Biomed Pharmacother* **2018**; 103: 1643-51. doi: 10.1016/j.biopha.2018.04.113.
7. de Mesquita LS, Luz TR, de Mesquita JW, Coutinho DF, do Amaral FM, de Sousa Ribeiro MN, et al. Exploring the anticancer properties of essential oils from family Lamiaceae. *Food Rev Int* **2019**; 35: 105-31. doi: 10.1080/87559129.2018.1467443.
8. Li Q, Yang S, Yang S, Xin F, Wang M. Anti-inflammatory activity of phlomisoside F isolated from *Phlomis younghusbandii* Mukerjee. *Int Immunopharmacol* **2015**; 28: 724-30. doi: 10.1016/j.intimp.2015.07.035.
9. Zhao B, Liang HX, Yu YF, Dong XP. [A new furanolabdane diterpene glycoside *from Phlomis younghusbandii* Mukerjee]. *Yao Xue Xue Bao* **2009**; 44: 60-2. [Chinese].
10. Lu XX, Ji XX, Bao J, Li QQ, Ji DD, Luo L. Inhibition of proliferation, migration and invasion of human non-small cell lung cancer cell line A549 by phlomisoside F from *Phlomis younghusbandii* Mukerjee. *Trop J Pharm Res* **2016**; 15: 1413-21. doi: 10.4314/tjpr.v15i7.9.
11. Shivapurkar N, Reddy J, Chaudhary PM, Gazdar AF. Apoptosis and lung cancer: a review. *J Cell Biochem* **2003**; 88: 885-98. doi: 10.1002/jcb.10440.
12. Thorburn A. Death receptor-induced cell killing. *Cell Signal* **2004**; 16: 139-44. doi: 10.1016/j.cellsig.2003.08.007.
13. Yon JH, Daniel-Johnson J, Carter LB, Jevtovic-Todorovic V. Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. *Neuroscience* **2005**; 135: 815-27. doi: 10.1016/j.neuroscience.2005.03.064.
14. Boatright KM, Salvesen GS. Mechanisms of caspase activation. *Curr Opin Cell Biol* **2003**; 15: 725-31. doi: 10.1016/j.ceb.2003.10.009.
15. Hong YS, Ham YA, Choi JH, Kim J. Effects of allyl sulfur compounds and garlic extract on the expression of Bcl-2, Bax, and p53 in non-small cell lung cancer cell lines. *Exp Mol Med* **2000**; 32: 127-34. doi: 10.1038/emm.2000.22.
16. Greenhough A, Smartt HJ, Moore AE, Roberts HR, Williams AC, Paraskeva C, et al. The COX-2/PGE2 pathway: key roles in the hallmarks of cancer and adaptation to the tumour microenvironment. *Carcinogenesis* **2009**; 30: 377-86. doi: 10.1093/carcin/bgp014.
17. Xiang L, Gao Y, Chen S, Sun J, Wu J, Meng X. Therapeutic potential of *Scutellaria baicalensis* Georgi in lung cancer therapy. *Phytomedicine* **2022**; 95: 153727. doi: 10.1016/j.phymed.2021.153727.
18. Xiang L, Gao Y, Chen S, Sun J, Wu J, Meng X. Therapeutic potential of *Scutellaria baicalensis* Georgi in lung cancer therapy. *Phytomedicine* **2022**; 95: 153727. doi: 10.1016/j.phymed.2021.153727.
19. Gao J, Morgan WA, Sanchez-Medina A, Corcoran O. The ethanol extract of *Scutellaria baicalensis* and the active compounds induce cell cycle arrest and apoptosis including upregulation of p53 and Bax in human lung cancer cells. *Toxicol Appl Pharmacol* **2011**; 254: 221-8. doi: 10.1016/j.taap.2011.03.016.
20. Alsharairi NA. *Scutellaria baicalensis* and their natural flavone compounds as potential medicinal drugs for the treatment of nicotine-induced non-small-cell lung cancer and asthma. *Int J Environ Res Public Health* **2021**; 18: 5243. doi: 10.3390/ijerph18105243.
21. Yousefi K, Hamedeyazdan S, Hodaei D, Lotfipour F, Baradaran

B, Orangi M, et al. An in vitro ethnopharmacological study on *Prangos ferulacea*: a wound healing agent. *Bioimpacts* **2017**; 7: 75-82. doi: 10.15171/bi.2017.10.
22. Park KI, Park HS, Kang SR, Nagappan A, Lee DH, Kim JA, et al. Korean *Scutellaria baicalensis* water extract inhibits cell cycle G1/S transition by suppressing cyclin D1 expression and matrix-metalloproteinase-2 activity in human lung cancer cells. *J Ethnopharmacol* **2011**; 133: 634-41. doi: 10.1016/j.jep.2010.10.057.
23. Kim HI, Hong SH, Ku JM, Lim YS, Lee SJ, Song J, et al. *Scutellaria radix* promotes apoptosis in non-small cell lung cancer cells via induction of AMPK-dependent autophagy. *Am J Chin Med* **2019**; 47: 691-705. doi: 10.1142/s0192415x19500368.
24. Wang Y, Cao HJ, Sun SJ, Dai JY, Fang JW, Li QH, et al. Total flavonoid aglycones extract in *Radix scutellariae* inhibits lung carcinoma and lung metastasis by affecting cell cycle and DNA synthesis. *J Ethnopharmacol* **2016**; 194: 269-79. doi: 10.1016/j.jep.2016.07.052.
25. Gong WY, Wu JF, Liu BJ, Zhang HY, Cao YX, Sun J, et al. Flavonoid components in *Scutellaria baicalensis* inhibit nicotine-induced proliferation, metastasis and lung cancer-associated inflammation in vitro. *Int J Oncol* **2014**; 44: 1561-70. doi: 10.3892/ijo.2014.2320.
26. Zhao Z, Liu B, Sun J, Lu L, Liu L, Qiu J, et al. *Scutellaria* flavonoids effectively inhibit the malignant phenotypes of non-small cell lung cancer in an Id1-dependent manner. *Int J Biol Sci* **2019**; 15: 1500-13. doi: 10.7150/ijbs.33146.
27. Park HJ, Park SH, Choi YH, Chi GY. The root extract of *Scutellaria baicalensis* induces apoptosis in EGFR TKI-resistant human lung cancer cells by inactivation of STAT3. *Int J Mol Sci* **2021**; 22: 5181. doi: 10.3390/ijms22105181.
28. Yin X, Zhou J, Jie C, Xing D, Zhang Y. Anticancer activity and mechanism of *Scutellaria barbata* extract on human lung cancer cell line A549. *Life Sci* **2004**; 75: 2233-44. doi: 10.1016/j.lfs.2004.05.015.
29. Liu J, Jiang M, Li Z, Zhang X, Li X, Hao Y, et al. A novel systems pharmacology method to investigate molecular mechanisms of *Scutellaria barbata* D. Don for non-small cell lung cancer. *Front Pharmacol* **2018**; 9: 1473. doi: 10.3389/fphar.2018.01473.
30. Wang Q, Acharya N, Liu Z, Zhou X, Cromie M, Zhu J, et al. Enhanced anticancer effects of *Scutellaria barbata* D. Don in combination with traditional Chinese medicine components on non-small cell lung cancer cells. *J Ethnopharmacol* **2018**; 217: 140-51. doi: 10.1016/j.jep.2018.02.020.
31. Yang X, Yang Y, Tang S, Tang H, Yang G, Xu Q, et al. Anti-tumor effect of polysaccharides from *Scutellaria barbata* D. Don on the 95-D xenograft model via inhibition of the C-met pathway. *J Pharmacol Sci* **2014**; 125: 255-63. doi: 10.1254/jphs.13276fp.
32. Shiau AL, Shen YT, Hsieh JL, Wu CL, Lee CH. *Scutellaria barbata* inhibits angiogenesis through downregulation of HIF-1 α in lung tumor. *Environ Toxicol* **2014**; 29: 363-70. doi: 10.1002/tox.21763.
33. Świąder K, Startek K, Wijaya CH. The therapeutic properties of lemon balm (*Melissa officinalis* L.): reviewing novel findings and medical indications. *J Appl Bot Food Qual* **2019**; 92: 327-5. doi: 10.5073/jabfq.2019.092.044.
34. Faraji P, Araj-Khodaei M, Ghaffari M, Ezzati Nazhad Dolatabadi J. Anticancer effects of *Melissa officinalis*: a traditional medicine. *Pharm Sci* **2021**; 28: 355-64. doi: 10.34172/ps.2021.43.
35. Jahanban-Esfahlan R, Seidi K, Monfaredan A, Shafie-Irannejad V, Mesgari Abbasi M, Karimian A, et al. The herbal medicine *Melissa officinalis* extract effects on gene expression of p53, Bcl-2, Her2, VEGF-A and hTERT in human lung, breast and prostate cancer cell lines. *Gene* **2017**; 613: 14-9. doi: 10.1016/j.gene.2017.02.034.
36. Jeung IC, Jee D, Rho CR, Kang S. *Melissa officinalis* L. extracts protect human retinal pigment epithelial cells against oxidative stress-induced apoptosis. *Int J Med Sci* **2016**; 13: 139-46. doi: 10.7150/ijms.13861.
37. de Sousa AC, Alviano DS, Blank AF, Alves PB, Alviano CS, Gattass CR. *Melissa officinalis* L. essential oil: antitumoral and antioxidant activities. *J Pharm Pharmacol* **2004**; 56: 677-81. doi: 10.1211/0022357023321.
38. Garjani A, Tila D, Hamedeyazdan S, Vaez H, Rameshrad M, Pashaii M, et al. An investigation on cardioprotective potential of *Marrubium vulgare* aqueous fraction against ischaemia-reperfusion injury in isolated rat heart. *Folia Morphol (Warsz)* **2017**; 76: 361-71. doi: 10.5603/FM.a2017.0011.
39. Moacă EA, Farcaş C, Ghiţu A, Coricovac D, Popovici R, Cărăba-Meiţă NL, et al. A comparative study of *Melissa officinalis* leaves and stems ethanolic extracts in terms of antioxidant, cytotoxic, and antiproliferative potential. *Evid Based Complement Alternat Med* **2018**; 2018: 7860456. doi: 10.1155/2018/7860456.
40. Ghazizadeh J, Sadigh-Eteghad S, Marx W, Fakhari A, Hamedeyazdan S, Torbati M, et al. The effects of lemon balm (*Melissa officinalis* L.) on depression and anxiety in clinical trials: a systematic review and meta-analysis. *Phytother Res* **2021**; 35: 6690-705. doi: 10.1002/ptr.7252.
41. Magalhães DB, Castro I, Lopes-Rodrigues V, Pereira JM, Barros L, Ferreira I, et al. *Melissa officinalis* L. ethanolic extract inhibits the growth of a lung cancer cell line by interfering with the cell cycle and inducing apoptosis. *Food Funct* **2018**; 9: 3134-42. doi: 10.1039/c8fo00446c.
42. Jahanban-Esfahlan A, Modaeinama S, Abasi M, Mesgari Abbasi M, Jahanban-Esfahlan R. Anti proliferative properties of *Melissa officinalis* in different human cancer cells. *Asian Pac J Cancer Prev* **2015**; 16: 5703-7. doi: 10.7314/apjcp.2015.16.14.5703.
43. Chen HM, Lee MJ, Kuo CY, Tsai PL, Liu JY, Kao SH. *Ocimum gratissimum* aqueous extract induces apoptotic signalling in lung adenocarcinoma cell A549. *Evid Based Complement Alternat Med* **2011**; 2011: 739093. doi: 10.1155/2011/739093.
44. Njoku CJ, Zeng L, Asuzu IU, Oberlies NH, McLaughlin JL. Oleanolic acid, a bioactive component of the leaves of *Ocimum Gratissimum* (Lamiaceae). *Int J Pharmacogn* **1997**; 35: 134-7. doi: 10.1076/phbi.35.2.134.13290.
45. Huang CC, Hwang JM, Tsai JH, Chen JH, Lin H, Lin GJ, et al. Aqueous *Ocimum gratissimum* extract induces cell apoptosis in human hepatocellular carcinoma cells. *Int J Med Sci* **2020**; 17: 338-46. doi: 10.7150/ijms.39436.
46. Baliga MS, Jimmy R, Thilakchand KR, Sunitha V, Bhat NR, Saldanha E, et al. *Ocimum sanctum* L (holy basil or tulsi) and its phytochemicals in the prevention and treatment of cancer. *Nutr Cancer* **2013**;65 Suppl 1:26-35. doi: 10.1080/01635581.2013.785010.
47. Wihadmadyatami H, Karnati S, Hening P, Tjahjono Y, Rizal, Maharjanti F, et al. Ethanolic extract *Ocimum sanctum* Linn. induces an apoptosis in human lung adenocarcinoma (A549) cells. *Heliyon* **2019**; 5: e02772. doi: 10.1016/j.heliyon.2019.e02772.
48. Sridevi M, Bright J, Yamini K. Anti-cancer effect of *Ocimum sanctum* ethanolic extract in non-small cell lung carcinoma cell line. *Int J Pharm Pharm Sci* **2016**; 8: 242-6.
49. Kwak TK, Sohn EJ, Kim S, Won G, Choi JU, Jeong K, et al. Inhibitory effect of ethanol extract of *Ocimum sanctum* on osteopontin mediated metastasis of NCI-H460 non-small cell lung cancer cells. *BMC Complement Altern Med* **2014**; 14: 419. doi: 10.1186/1472-6882-14-419.
50. Joseph B, Nair VM. *Ocimum sanctum* Linn. (holy basil): pharmacology behind its anti-cancerous effect. *Int J Pharma Bio Sci* **2013**; 4: 556-75.
51. Kustiati U, Ratih TSD, Agung ND, Kusindarta DL, Wihadmadyatami H. In silico molecular docking and in vitro analysis of ethanolic extract *Ocimum sanctum* Linn.: inhibitory and apoptotic effects against non-small cell lung cancer. *Vet World* **2021**; 14: 3175-87. doi: 10.14202/vetworld.2021.3175-3187.
52. Kim SC, Magesh V, Jeong SJ, Lee HJ, Ahn KS, Lee HJ, et al. Ethanol extract of *Ocimum sanctum* exerts anti-metastatic activity through inactivation of matrix metalloproteinase-9 and enhancement of anti-oxidant enzymes. *Food Chem Toxicol* **2010**; 48: 1478-82. doi: 10.1016/j.fct.2010.03.014.
53. Bouyahya A, Guaouguaou FE, Dakka N, Bakri Y. Pharmacological activities and medicinal properties of endemic Moroccan medicinal plant *Origanum compactum* (Benth) and their main compounds. *Asian Pac J Trop Dis* **2017**; 7: 628-40. doi: 10.12980/apjtd.7.2017D7-31.

54. Bouyahya A, Jamal A, Edaoudi F, Et-Touys A, Bakri Y, Dakka N. *Origanum compactum* Benth: a review on phytochemistry and pharmacological properties. *Med Aromat Plants* **2016**; 5: 252. doi: 10.4172/2167-0412.1000252.
55. Chaouki W, Meddah B, Hmamouchi M. Antiproliferative activity of *Origanum compactum* extract on lung cancer and hepatoma cells. *Arab J Med Aromat Plants* **2015**; 1:44-56. doi: 10.48347/IMIST.PRSM/ajmap-v1i1.3257.
56. Chen X, Guo J, Bao J, Lu J, Wang Y. The anticancer properties of *Salvia miltiorrhiza* Bunge (Danshen): a systematic review. *Med Res Rev* **2014**; 34: 768-94. doi: 10.1002/med.21304.
57. Yuan SL, Wei YQ, Wang XJ, Xiao F, Li SF, Zhang J. Growth inhibition and apoptosis induction of tanshinone II-A on human hepatocellular carcinoma cells. *World J Gastroenterol* **2004**; 10: 2024-8. doi: 10.3748/wjg.v10.i14.2024.
58. Dai ZK, Qin JK, Huang JE, Luo Y, Xu Q, Zhao HL. Tanshinone IIA activates calcium-dependent apoptosis signaling pathway in human hepatoma cells. *J Nat Med* **2012**; 66: 192-201. doi: 10.1007/s11418-011-0576-0.
59. Zhou L, Chan WK, Xu N, Xiao K, Luo H, Luo KQ, et al. Tanshinone IIA, an isolated compound from *Salvia miltiorrhiza* Bunge, induces apoptosis in HeLa cells through mitotic arrest. *Life Sci* **2008**; 83: 394-403. doi: 10.1016/j.lfs.2008.07.011.
60. Liu F, Yu G, Wang G, Liu H, Wu X, Wang Q, et al. An NQO1-initiated and p53-independent apoptotic pathway determines the anti-tumor effect of tanshinone IIA against non-small cell lung cancer. *PLoS One* **2012**; 7: e42138. doi: 10.1371/journal.pone.0042138.
61. Sun Y, Xun K, Wang Y, Chen X. A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. *Anticancer Drugs* **2009**; 20: 757-69. doi: 10.1097/CAD.0b013e328330d95b.
62. Chen XP, Pei LX, Wang YT. Discussion on research and development models in innovative Chinese materia medica. *Chin Tradit Herb Drugs* **2011**; 42: 1255-60.
63. Park IJ, Kim MJ, Park OJ, Park MG, Choe W, Kang I, et al. Cryptotanshinone sensitizes DU145 prostate cancer cells to Fas(APO1/CD95)-mediated apoptosis through Bcl-2 and MAPK regulation. *Cancer Lett* **2010**; 298: 88-98. doi: 10.1016/j.canlet.2010.06.006.
64. Lee CY, Sher HF, Chen HW, Liu CC, Chen CH, Lin CS, et al. Anticancer effects of tanshinone I in human non-small cell lung cancer. *Mol Cancer Ther* **2008**; 7: 3527-38. doi: 10.1158/1535-7163.mct-07-2288.
65. Li Y, Gong Y, Li L, Abdolmaleky HM, Zhou JR. Bioactive tanshinone I inhibits the growth of lung cancer in part via downregulation of Aurora A function. *Mol Carcinog* **2013**; 52: 535-43. doi: 10.1002/mc.21888.
66. Tung YT, Chen HL, Lee CY, Chou YC, Lee PY, Tsai HC, et al. Active component of Danshen (*Salvia miltiorrhiza* Bunge), tanshinone I, attenuates lung tumorigenesis via inhibitions of VEGF, cyclin A, and cyclin B expressions. *Evid Based Complement Alternat Med* **2013**; 2013: 319247. doi: 10.1155/2013/319247.
67. Dat NT, Jin X, Lee JH, Lee D, Hong YS, Lee K, et al. Abietane diterpenes from *Salvia miltiorrhiza* inhibit the activation of hypoxia-inducible factor-1. *J Nat Prod* **2007**; 70: 1093-7. doi: 10.1021/np060482d.
68. Lee DS, Lee SH, Kwon GS, Lee HK, Woo JH, Kim JG, et al. Inhibition of DNA topoisomerase I by dihydrotanshinone I, components of a medicinal herb *Salvia miltiorrhiza* Bunge. *Biosci Biotechnol Biochem* **1999**; 63: 1370-3. doi: 10.1271/bbb.63.1370.
69. Cao HY, Ding RL, Li M, Yang MN, Yang LL, Wu JB, et al. Danshensu, a major water-soluble component of *Salvia miltiorrhiza*, enhances the radioresponse for Lewis lung carcinoma xenografts in mice. *Oncol Lett* **2017**; 13: 605-12. doi: 10.3892/ol.2016.5508.
70. Ye YT, Zhong W, Sun P, Wang D, Wang C, Hu LM, et al. Apoptosis induced by the methanol extract of *Salvia miltiorrhiza* Bunge in non-small cell lung cancer through PTEN-mediated inhibition of PI3K/Akt pathway. *J Ethnopharmacol* **2017**; 200: 107-16. doi: 10.1016/j.jep.2016.12.051.
71. Tian H, Li Y, Mei J, Cao L, Yin J, Liu Z, et al. Effects of *Salvia miltiorrhiza* extract on lung adenocarcinoma. *Exp Ther Med* **2021**; 22: 794. doi: 10.3892/etm.2021.10226.
72. Rashid A, Liu C, Sanli T, Tsiani E, Singh G, Bristow RG, et al. Resveratrol enhances prostate cancer cell response to ionizing radiation. Modulation of the AMPK, Akt and mTOR pathways. *Radiat Oncol* **2011**; 6: 144. doi: 10.1186/1748-717x-6-144.
73. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **1997**; 275: 218-20. doi: 10.1126/science.275.5297.218.
74. Moore J, Megaly M, MacNeil AJ, Klentrou P, Tsiani E. Rosemary extract reduces Akt/mTOR/p70S6K activation and inhibits proliferation and survival of A549 human lung cancer cells. *Biomed Pharmacother* **2016**; 83: 725-32. doi: 10.1016/j.biopha.2016.07.043.
75. Ulubelen A, Topçu G, Chai HB, Pezzuto JM. Cytotoxic activity of diterpenoids isolated from *Salvia hypargeia*. *Pharm Biol* **1999**; 37: 148-51. doi: 10.1076/phbi.37.2.148.6082.
76. Tundis R, Loizzo MR, Menichini F, Bonesi M, Colica C, Menichini F. In vitro cytotoxic activity of extracts and isolated constituents of *Salvia leriifolia* Benth. against a panel of human cancer cell lines. *Chem Biodivers* **2011**; 8: 1152-62. doi: 10.1002/cbdv.201000311.
77. Sabarinathan D, Mahalakshmi P, Vanisree AJ. Naringenin promote apoptosis in cerebrally implanted C6 glioma cells. *Mol Cell Biochem* **2010**; 345: 215-22. doi: 10.1007/s11010-010-0575-6.
78. Zhang JS, Ding J, Tang QM, Li M, Zhao M, Lu LJ, et al. Synthesis and antitumour activity of novel diterpenequinone salvicine and the analogs. *Bioorg Med Chem Lett* **1999**; 9: 2731-6. doi: 10.1016/s0960-894x(99)00472-2.
79. Meng LH, Zhang JS, Ding J. Salvicine, a novel DNA topoisomerase II inhibitor, exerting its effects by trapping enzyme-DNA cleavage complexes. *Biochem Pharmacol* **2001**; 62: 733-41. doi: 10.1016/s0006-2952(01)00732-8.
80. Chang J, Xu J, Li M, Zhao M, Ding J, Zhang JS. Novel cytotoxic seco-abietane rearranged diterpenoids from *Salvia prionitis*. *Planta Med* **2005**; 71: 861-6. doi: 10.1055/s-2005-871279.
81. Xia F, Wu CY, Yang XW, Li X, Xu G. Diterpenoids from the roots of *Salvia yunnanensis*. *Nat Prod Bioprospect* **2015**; 5: 307-12. doi: 10.1007/s13659-015-0080-4.
82. Wu CY, Liao Y, Yang ZG, Yang XW, Shen XL, Li RT, et al. Cytotoxic diterpenoids from *Salvia yunnanensis*. *Phytochemistry* **2014**; 106: 171-7. doi: 10.1016/j.phytochem.2014.07.001.
83. Erbano M, Ehrenfried CA, Stefanello M, Dos Santos EP. Morphoanatomical and phytochemical studies of *Salvia lachnostachys* (Lamiaceae). *Microsc Res Tech* **2012**; 75: 1737-44. doi: 10.1002/jemt.22125.
84. Oliveira CS, Barison A, Santos EP, Carvalho JE, Salvador MJ, Stefanello ME. Isolation of Diterpenes of *Salvia lachnostachys* Guided by Antiproliferative Assays Against Human Tumour Cells. Available from: http://anais.infobibos.com.br/bcnp/Abstracts/ResumoBCNP_185.pdf.
85. Esquivel B, Bustos-Brito C, Sánchez-Castellanos M, Nieto-Camacho A, Ramírez-Apan T, Joseph-Nathan P, et al. Structure, absolute configuration, and antiproliferative activity of abietane and icetexane diterpenoids from *Salvia ballotiflora*. *Molecules* **2017**; 22: 1690. doi: 10.3390/molecules22101690.
86. Campos-Xolalpa N, Alonso-Castro ÁJ, Sánchez-Mendoza E, Zavala-Sánchez MÁ, Pérez-Gutiérrez S. Cytotoxic activity of the chloroform extract and four diterpenes isolated from *Salvia ballotiflora*. *Rev Bras Farmacogn* **2017**; 27: 302-5. doi: 10.1016/j.bjp.2017.01.007.
87. Liu DM, Cao ZX, Yan HL, Li W, Yang F, Zhao WJ, et al. A new abietane diterpenoid from *Ajuga ovalifolia* var. *calantha* induces human lung epithelial A549 cell apoptosis by inhibiting SHP2. *Fitoterapia* **2020**; 141: 104484. doi: 10.1016/j.fitote.2020.104484.
88. Yan H, Jiang M, Yang F, Tang X, Lin M, Zhou C, et al. Ajuforrestin A, an abietane diterpenoid from *Ajuga ovalifolia* var. *calanthe*, induces A549 cell apoptosis by targeting SHP2. *Molecules* **2022**;

27: 5469. doi: 10.3390/molecules27175469.
89. Wan J, Liu M, Jiang HY, Yang J, Du X, Li XN, et al. Bioactive ent-kaurane diterpenoids from *Isodon serra*. *Phytochemistry* **2016**; 130: 244-51. doi: 10.1016/j.phytochem.2016.05.014.
90. Wang JN, Zhang ZR, Che Y, Yuan ZY, Lu ZL, Li Y, et al. Acetylmacrocalin B, an ent-kaurane diterpenoid, initiates apoptosis through the ROS-p38-caspase 9-dependent pathway and induces G2/M phase arrest via the Chk1/2-Cdc25C-Cdc2/cyclin B axis in non-small cell lung cancer. *Cancer Biol Ther* **2018**; 19: 609-21. doi: 10.1080/15384047.2018.1449613.
91. Ali MA, Abul Farah M, Al-Hemaid FM, Abou-Tarboush FM. In vitro cytotoxicity screening of wild plant extracts from Saudi Arabia on human breast adenocarcinoma cells. *Genet Mol Res* **2014**; 13: 3981-90. doi: 10.4238/2014.May.23.9.
92. Justus B, Kanunfre CC, Budel JM, de Faria MF, Raman V, de Paula JP, et al. New insights into the mechanisms of French lavender essential oil on non-small-cell lung cancer cell growth. *Ind Crops Prod* **2019**; 136: 28-36. doi: 10.1016/j.indcrop.2019.04.051.
93. Praveena B, Pradeep S N. Antioxidant and antibacterial activities in the leaf extracts of Indian borage (*Plectranthus amboinicus*). *Food Nutr Sci* **2012**; 3: 146-52. doi: 10.4236/fns.2012.32022.
94. George AZ, Anil K, Calistus Jude AL, Srinivasan, Srinivasa Sundar Rajan R. A study on the cytotoxicity of *Plectranthus amboinicus* and *Bacopa monnieri* stem extracts on lung cancer cell line. *Curr Trends Biotechnol Pharm* **2021**; 15: 395-400. doi: 10.5530/ctbp.2021.3s.31.
95. Yin QH, Yan FX, Zu XY, Wu YH, Wu XP, Liao MC, et al. Anti-proliferative and pro-apoptotic effect of carvacrol on human hepatocellular carcinoma cell line HepG-2. *Cytotechnology* **2012**; 64: 43-51. doi: 10.1007/s10616-011-9389-y.
96. Manjamalai A, Grace VM. The chemotherapeutic effect of essential oil of *Plectranthus amboinicus* (Lour) on lung metastasis developed by B16F-10 cell line in C57BL/6 mice. *Cancer Invest* **2013**; 31: 74-82. doi: 10.3109/07357907.2012.749268.
97. Tran LT, Ho DV, Le DV, Hung TM, Nguyen HT, Raal A. Three new phloroglucinol derivatives from the aerial parts of *Pogostemon auricularius* and their cytotoxic activity. *Phytochem Lett* **2018**; 28: 88-92. doi: 10.1016/j.phytol.2018.09.016.
98. Tran LTT, Ho DV, Le DV, Van Phan K, Nguyen HT, Raal A. Apoptosis-inducing effect of pogostemin A isolated from the aerial parts of *Pogostemon auricularius* against the human lung cancer cells. *J Biol Act Prod Nat* **2019**; 9: 320-7. doi: 10.1080/22311866.2019.1687334.
99. Punfa W, Khanaree C, Pintha K, Chumphukam O, Suttajit M, Tantipaiboonwong P. Protective effect of *Perilla* leaf extract against ROS formation and inflammation induced by TNF-α in A549 human lung carcinoma cell line. *Songklanakarin J Sci Technol* **2022**; 44: 361-9.
100. Pintha K, Chaiwangyen W, Yodkeeree S, Suttajit M, Tantipaiboonwong P. Suppressive effects of rosmarinic acid rich fraction from *Perilla* on oxidative stress, inflammation and metastasis ability in A549 Cells Exposed to PM via C-Jun, P-65-Nf-Kb and Akt signaling pathways. *Biomolecules* **2021**; 11: 1090. doi: 10.3390/biom11081090.
101. Abd El-Hafeez AA, Fujimura T, Kamei R, Hirakawa N, Baba K, Ono K, et al. A methoxyflavanone derivative from the Asian medicinal herb (*Perilla frutescens*) induces p53-mediated G2/M cell cycle arrest and apoptosis in A549 human lung adenocarcinoma. *Cytotechnology* **2018**; 70: 899-912. doi: 10.1007/s10616-017-0116-1.
102. Abd El-Hafeez AA, Fujimura T, Kamei R, Hirakawa N, Baba K, Ono K, et al. Synergistic tumor suppression by a *Perilla frutescens*-derived methoxyflavanone and anti-cancer tyrosine kinase inhibitors in A549 human lung adenocarcinoma. *Cytotechnology* **2018**; 70: 913-9. doi: 10.1007/s10616-017-0124-1.
103. Kwak Y, Ju J. Inhibitory activities of *Perilla frutescens* Britton leaf extract against the growth, migration, and adhesion of human cancer cells. *Nutr Res Pract* **2015**; 9: 11-6. doi: 10.4162/nrp.2015.9.1.11.
104. Sun Z, Wang H, Wang J, Zhou L, Yang P. Chemical composition and anti-inflammatory, cytotoxic and antioxidant activities of essential oil from leaves of *Mentha piperita* grown in China. *PLoS One* **2014**; 9: e114767. doi: 10.1371/journal.pone.0114767.
105. Farnam G, Aryanpour N, Behtaj R, Hosseini Shirazi F. Cytotoxic and cell progression effects of *Mentha pulegium* L extract on selected cancer cell lines: cytotoxicity of *Mentha pulegium* L extract on selected cancer cell lines. *Iran J Pharm Sci* **2020**; 16: 27-34. doi: 10.22037/ijps.v16.40423.
106. Sharma V, Hussain S, Gupta M, Saxena AK. In vitro anticancer activity of extracts of *Mentha* spp. against human cancer cells. *Indian J Biochem Biophys* **2014**; 51: 416-9.
107. Fang XQ, Kim YS, Lee YM, Lee M, Lim WJ, Yim WJ, et al. *Polygonum cuspidatum* extract (Pc-Ex) containing emodin suppresses lung cancer-induced cachexia by suppressing TCF4/TWIST1 complex-induced PTHrP expression. *Nutrients* **2022**; 14: 1508. doi: 10.3390/nu14071508.
108. Lin YW, Yang FJ, Chen CL, Lee WT, Chen RS. Free radical scavenging activity and antiproliferative potential of *Polygonum cuspidatum* root extracts. *J Nat Med* **2010**; 64: 146-52. doi: 10.1007/s11418-009-0387-8.
109. Kimura Y, Okuda H. Resveratrol isolated from *Polygonum cuspidatum* root prevents tumor growth and metastasis to lung and tumor-induced neovascularization in Lewis lung carcinoma-bearing mice. *J Nutr* **2001**; 131: 1844-9. doi: 10.1093/jn/131.6.1844.
110. Xin H, Kong Y, Wang Y, Zhou Y, Zhu Y, Li D, et al. Lignans extracted from *Vitex negundo* possess cytotoxic activity by G2/M phase cell cycle arrest and apoptosis induction. *Phytomedicine* **2013**; 20: 640-7. doi: 10.1016/j.phymed.2013.02.002.
111. Fan J, Bao Y, Meng X, Wang S, Li T, Chang X, et al. Mechanism of modulation through PI3K-AKT pathway about *Nepeta cataria* L.'s extract in non-small cell lung cancer. *Oncotarget* **2017**; 8: 31395-405. doi: 10.18632/oncotarget.15608.
112. Oliviero M, Romilde I, Beatrice MM, Matteo V, Giovanna N, Consuelo A, et al. Evaluations of thyme extract effects in human normal bronchial and tracheal epithelial cell lines and in human lung cancer cell line. *Chem Biol Interact* **2016**; 256: 125-33. doi: 10.1016/j.cbi.2016.06.024.
113. Nikolić M, Glamočlija J, Ferreira ICFR, Calhelha RC, Fernandes Â, Marković T, et al. Chemical composition, antimicrobial, antioxidant and antitumor activity of *Thymus serpyllum* L., *Thymus algeriensis* Boiss. and Reut and *Thymus vulgaris* L. essential oils. *Ind Crops Prod* **2014**; 52: 183-90. doi: 10.1016/j.indcrop.2013.10.006.
114. Zu Y, Yu H, Liang L, Fu Y, Efferth T, Liu X, et al. Activities of ten essential oils towards Propionibacterium acnes and PC-3, A-549 and MCF-7 cancer cells. *Molecules* **2010**; 15: 3200-10. doi: 10.3390/molecules15053200.
115. Basappa G, Kumar V, Sarojini BK, Poornima DV, Gajula H, Sannabommaji TK, et al. Chemical composition, biological properties of *Anisomeles indica* Kuntze essential oil. *Ind Crops Prod* **2015**; 77: 89-96. doi: 10.1016/j.indcrop.2015.08.041.
116. Yu CY, Jerry Teng CL, Hung PS, Cheng CC, Hsu SL, Hwang GY, et al. Ovatodiolide isolated from *Anisomeles indica* induces cell cycle G2/M arrest and apoptosis via a ROS-dependent ATM/ATR signaling pathways. *Eur J Pharmacol* **2018**; 819: 16-29. doi: 10.1016/j.ejphar.2017.09.050.
117. Pathania AS, Guru SK, Verma MK, Sharma C, Abdullah ST, Malik F, et al. Disruption of the PI3K/AKT/mTOR signaling cascade and induction of apoptosis in HL-60 cells by an essential oil from *Monarda citriodora*. *Food Chem Toxicol* **2013**; 62: 246-54. doi: 10.1016/j.fct.2013.08.037.
118. Haidara K, Alachkar A, Al Moustafa AE. *Teucrium polium* plant extract provokes significant cell death in human lung cancer cells. *Health* **2011**; 3: 366-9. doi: 10.4236/health.2011.36062.