Immunopathologia Persa
http immunopathol.com
DOI:10.34172/ipp.2022.38455

Medical plants for lung cancer: an overview of current knowledge

Mohammadreza Khosravifarsani[1], Ramin Tolouian[2], Sepideh Yadollahifarsani[3], Parisa Soleimani[4], Marni Sarazen[5], Pouria Mostafizi[6], Audrey Tolouian[7*], Anil K. Philip[8], Zahra Golestani Hotkani[9]

[1]Cancer Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran
[2]Southern Arizona VA Health Care System and College of Medicine, University of Arizona, Tucson, AZ, USA
[3]Independent Researcher, Isfahan, Iran
[4]Nickan Research Institute, Isfahan, Iran
[5]Department of Internal Medicine, College of Medicine, University of Arizona, Tucson, Arizona, USA
[6]Department of Physiology, College of Medicine, University of Arizona, Tucson, AZ, USA
[7]Holistic Nursing Program, Northern New Mexico College, Espanola, New Mexico, USA
[8]School of Pharmacy, College of Pharmacy and Nursing, University of Nizwa, Nizwa, Sultanate of Oman
[9]Department of Bioscience, University of Milan, Milan, Italy

***Correspondence to**
Audrey Tolouian,
Email:
audrey.tolouian@nnmc.edu

Received 22 Oct. 2022
Accepted 22 Dec. 2022
Published online 24 Dec. 2022

Keywords: Lung cancer, Anticancer agents, Medicinal plants, Cell growth, Malignant cells, Phytochemical compounds, Reactive oxygen species, Pulmonary malignancy

Abstract

Lung cancer is an uncontrolled cell growth in lung tissue, with changes in the cellular, epigenetic and genetic alterations, oncogenes activation and clonal evolution of malignant cells. The most critical risk factor for lung cancer is cigarette smoking (80-85%). Other reasons for lung cancer (15-20%) include genetic factors, exposure to secondhand smoke, air pollution, radiation, hazardous gases and foreign chemical agents. The most widely used strategies in lung cancer treatment are chemotherapy, radiotherapy and surgery. However, there are various adverse effects, such as significant toxicity, limited efficiency and multidrug resistance. Plants and plant-derived products have proven to have a role in lung cancer therapy and prevention through sensitizing conventional factors, extending patient survival time, avoiding adverse effects of chemotherapy, promoting physiological improvement and ameliorating quality of life in pulmonary malignancy cases. For this review article, we searched Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar, using various keywords. There are several natural product molecules with anticancer properties through many molecular mechanisms, including, inducing apoptosis, inhibition of angiogenesis and metastasis, reversion of multidrug resistance and also targeting reactive oxygen species signaling. Some phytochemical compounds are discussed as anticancer agents for lung cancer.

Citation: Khosravifarsani M, Tolouian R, Yadollahifarsani S, Soleimani P, Sarazen M, Mostafizi P, Tolouian A, Philip AK, Golestani Hotkani Z. Medical plants for lung cancer: an overview of current knowledge. Immunopathol Persa. 2023;9(1):e38455. DOI:10.34172/ipp.2022.38455.

Introduction

Lung cancer is the primary source of global cancer occurrence and mortality, accounting for approximately a quarter of all cancer cases (10 million deaths globally). The World Health Organization evaluated in 2020 that lung cancer affected 1.8 million deaths and registered 2.21 million new cases globally (1). Lung cancer is an uncontrolled cell growth in lung tissue with a high mortality rate. Most of the time, when the diagnosis is made, it has spread beyond a curable stage and cannot be treated surgically or with radiotherapy. Lung cancer is a multistage process induced by cellular, epigenetic and genetic changes. Those changes eventually ensue, oncogene activation, and clonal evolution of malignant cells (2).

The most critical risk factor for lung cancer is active cigarette smoking (80-85%) (3).

Key point

The natural product molecules with anticancer activities have the molecular mechanisms for developing anti-malignancy therapies, inducing apoptosis, inhibiting angiogenesis and metastasis, reversing multidrug resistance, and targeting reactive oxygen species signaling.

Other reasons for lung cancer (15-20%) include genetic alteration, passive smoking, air pollution, radiation, hazardous gases, and foreign chemical agents, for example, vinyl chloride, arsenic, cadmium, beryllium, chloride and nickel chromates (3).

Lung cancer is categorized into non-small cell lung carcinoma (NSCLC), which displays 80% of all lung cancer cases, including squamous cell carcinoma (SCC), adenocarcinoma (AD), and large cell

carcinoma (LCC), and finally, small cell lung carcinoma (SCLC) (4).

The most widely used strategies in lung cancer treatment are surgery, chemotherapy, and radiotherapy. Among these modalities, the most conducted method is chemotherapy which is associated with several complications, consisting limited efficacy, multidrug resistance and significant toxicity (1). Plants are recognized as one of the attractive approaches for lung cancer treatment since it has proven to be valuable and effective in sensitizing conventional agents, elongating patient survival time, preventing side effects of chemotherapy, promoting physiological improvement, and improving quality of life in pulmonary malignancy cases (5). Plant-derived phytochemicals selectively target cancer cells without affecting healthy cells, even in small amounts.

It has been shown that diet and natural agents from fruits and vegetables play an essential role in the prevention of malignancy in Western countries (1). Certain micronutrients (vitamins and minerals) and phytochemicals (carotenoids and phenols) have potent antioxidant or methyl-donating properties and thus have taken extensive attention. Previous studies also showed a reduced risk of pulmonary malignancy following the intake of some nutrient between smokers (1).

The concept of chemoprevention would benefit persons at high risk for developing lung cancer, such as heavy smokers, ex-smokers and patients with resected primary lung cancer.

Search strategy

For this review, we searched the Web of Science, EBSCO, Scopus, PubMed/Medline, DOAJ (Directory of Open Access Journals), Embase, and Google Scholar, using various keywords: lung cancer, anticancer agents, medicinal plants, cell growth, malignant cells, phytochemical compounds and reactive oxygen species.

Mechanisms of natural product molecules versus pulmonary malignancy

Plant-based herbal medicines are proposed as an efficient approach to pulmonary malignancy treatment (6). The mechanisms of action of natural product molecules in anticancer activities are mediated via inducing apoptosis, inhibiting angiogenesis and metastasis, reversion of multidrug resistance, and targeting reactive oxygen species (ROS) signaling (1,5).

Inducing apoptosis in malignant cells

Apoptosis, or programmed cell death, is a highly effective mechanism for killing malignant cells. Targeting apoptosis has been shown to be an effective non-surgical treatment for all types of cancers (4,5). Apoptosis includes a set of morphological changes, for example, cell shrinkage and blebbing of the plasma membrane. Apoptosis can be induced by preventing survival proteins such as NF-κB (kappa-light-chain-enhancer of activated B cells), Akt, Bcl-2 (B-cell lymphoma 2), and survivin in H460 cells. Some traditional herbs, such as the fruit and roots of *Toona sinensis, Ocimum gratissimum*, and acutiaporberine, have stimulated apoptosis in pulmonary neoplastic cells (4,5,7).

Inhibitory effects on angiogenesis and metastasis

Among the contributing parameters to the spread and growth of pulmonary malignancy, angiogenesis and metastasis are the most critical processes. Angiogenesis is an important process since it involves the development of new blood vessels from old vessels. In contrast, metastasis involves tumor cell intravasation, invasion and dissociation then form new tumors in other parts of the body. Thus, angiogenesis and metastasis blockage are two significant therapeutic targets for lung cancer. Some traditional herbs have anti-angiogenesis properties in lung cancer cells, such as *Ganoderma lucidum*, curcumin, green tea, and zingiber officinalis. Some plants have been categorized into alkaloids, flavonoids, terpenes, quinones, phenolics, xanthone, sulfur compounds and their chemical structures. These substances have favorable anti-metastasis activities by withholding key molecular factors supporting cell aggressiveness (8). The molecular mechanisms of potential naturally derived compounds in the control of metastatic lung cancer have been shown to have promising activities (9).

Reversion of multidrug resistance

The main problem of chemotherapy for patients is polydrug resistance (PDR) (10). One of the main mechanisms that induces PDR is cellular overproduction of p-glycoprotein to transfer the chemo agent back out of the cell. Several PDR reversal agents have been investigated by preventing the p-glycoprotein function, but their side effects profile was substantial (11).

Targeting reactive oxygen species signaling

Reactive oxygen species signaling is the focus of many researchers who work in the area of cancer. ROS signaling is the prime catalyst for the promotion and progression of many tumors, and targeting ROS signaling is a notable method in lung cancer treatments.

It has been suggested that histone deacetylase can significantly can adjust the oxidative stress in the progress of cancer in NSCLC (12). Histone deacetylase can be found in numerous common foods, such as sulforaphane, curcumin, and epigallocatechin 3-gallate (EGCG).

Previously, Zhai et al summarized current evidence directing fundamental etiological changes (e.g., DNA damage and epigenetics change) and lung function impairment that led to the development of lung cancer and adequate nutrition for it, such as vitamin C, vitamin B group and phytochemicals (13). It has been shown that cryptoxanthin supplementation and combined antioxidant administration (beta-carotene, alpha-tocopherol, and

ascorbic acid) mitigated oxidative DNA damage and had antioxidant effects (14). Some phytochemicals, like flavonoids, polyphenols and hydroxycinnamates have been shown to have anticancer and antioxidant efficacy. Moreover, experimental models demonstrated that polyphenols attach to electrophilic metabolites from carcinogens, prevent the production of oxygen radicals, lipid peroxidation, DNA oxidative damage and increase the detoxifying enzymes like the phase II enzymes, glucuronosyl transferases and glutathione transferases (15). Phytochemicals significantly inhibit pro-inflammatory parameters, consisting cyclooxygenase, xanthine oxidase and lipoxygenase-5, thus inhibiting tumor cell proliferation (16). Few reports suggest that phytochemicals such as EGCG might decrease ornithine decarboxylase activity that supports tumor cell proliferation and is induced by the procarcinogens intervention, which leads to reducing the synthesis of polyamine, protein, DNA and inhibits angiogenesis and induce apoptosis (17).

A systematic review by Kwon et al assessed the effectiveness and safety of herbal medicines for cancer-induced fatigue in 861 lung cancer patients. It has been observed that herbal medicines combined with conventional medicine significantly improved fatigue levels, quality of life, and activities of daily living compared to traditional medicine alone (18).

Likewise, Surien et al, investigated genomic modifications and herbal compounds as chemotherapeutic and chemoprevention agents, which specifically influence each subtype of lung cancer, such as adenocarcinoma, SCC and LCC (4).

Several marker-based treatments have been investigated for pulmonary malignancies, such as the vascular endothelial growth factor receptor-2/epidermal growth factor receptor inhibition, cell-cycle arrest, echinoderm protein-like 4–anaplastic lymphoma kinase fusion gene (EML4-ALK), miRNA modulation, iNOS suppression, hTERT silencing and KRAS (Kirsten rat sarcoma viral oncogene), angiotensin receptor blockade, V-Raf murine sarcoma viral oncogene homologue B1 (BRAF), chitin inhibition, WNT pathway, nuclear factor erythroid 2-related factor 2 activation, transforming growth factor beta antagonism, STAT3 (signal transducer and activator of transcription-3) pathway inhibition, and the role of p53 gene (19). It is recognized that there are numerous diagnostic, prognostic, and predictive biomarkers in lung cancer. Medicinal plants such as phytochemicals have shown promising results in targeting lung cancer biomarkers and opened an area for new investigation and drug development (20,21).

Meanwhile, Monteiro et al showed herbal medicines, have anti-proliferative activity against different types of lung cancer in animal models (22). It showed that pulmonary cancer might be inhibited by a diet rich in vegetables or fruits since they are supplemented with various dietary antioxidant polyphenols, like lignans, stilbenes, proanthocyanidins, flavonoids and phenolic acids. They showed an inverse association between lung cancer risk and consumption of vegetables and fruits in the daily diet in high-risk populations for lung cancer, such as smokers.-

Moreover, Singh et al summarized the chemical classification, mode of action of the phytochemicals in the mentioned plant species, and showed their role in the therapy of pulmonary neoplasms, including apoptosis, progression, metastasis and finally multidrug resistance (21). Additionally, several plant species include *Polygonum cuspidatum*, wampee, *Toona sinensis, Ocimum gratissimum,* Fabaceae family, *Scutellaria baicalensis*, and Solanaceae family, are detected in their study to cure lung cancer.

The extracts of *Polygonum cuspidatum* inhibit free-radical molecules such as DPPH (2,2-diphenyl-1-picrylhydrazyl) and hydroxyl in lung cancer cells such as H1650 and A549 (23). It is shown that the extract of wampee has higher antioxidant and anticancer effects against cisplatin in the lung cancer cell line of A549 (24). The extract of *Toona sinensis* leaf has an inhibitory consequence on ROS generation and induces apoptosis in pulmonary adenocarcinoma cells, especially H441 (25). Similarly, *Ocimum gratissimum* increases the activity of caspase-3 and 9 and antibacterial activities in lung cancer A549 cells (26). Some phytochemicals such as ursolic acid, acacetin, dihydroartemisinin, triptolide and acutiaporberine induce apoptosis. The Fabaceae family-derived acacetin increases p21 and p53 proteins, leading to the initiation of cell-cycle arrest and then apoptosis (27). Furthermore, *Scutellaria baicalensis* has anti-hypertensive, anti-metastatic, anti-febrifuge and anti-neoplasm effects with increased expression of PAI-1 (plasminogen activator inhibitor-1) and decreasing the expression of matrix metalloproteinase-2 and 9 (28). One cause of the failure of chemotherapy in pulmonary neoplasm is PDR. The phytochemicals, such as Solanaceae family-derived solamargine, are also reported as PDR reversal agents that increase the cytotoxic activity of epirubicin and trastuzumab against the pulmonary neoplastic cells such as H661 and H69 (29).

Anti-lung cancer natural product molecules in the body

A comprehensive review by Heng et al proposed potential clinical usage of phytochemical compounds, including curcumin, quercetin, epigallocatechin-3-gallate, resveratrol, luteolin, berberine, sulforaphane, genistein, and capsaicin as chemo preventive and anticancer agents for lung cancer (30).

The anticancer activities of phytochemicals in treating lung cancer with the ethnopharmacological effects on metastasis, angiogenesis, apoptosis, and clinical trial efficiency have been reviewed (7).

Some phytochemical compounds are discussed as anticancer agents for lung cancer as follows;

Green tea polyphenols and pulmonary malignancies

Some case-control investigations have studied the impacts of green tea drinking on pulmonary malignancies. Green tea consumption was associated with a decline in ROS signaling and abridged lung cancer risk amid non-smoking females (31).

Isothiocyanates

Cruciferous vegetables are rich in natural compounds of isothiocyanates, which are detected by their anticancer activity, anti-oxidant activity, and apoptosis-inducing. Likewise, isothiocyanates efficiently induce apoptosis and autophagy and prevent the proliferation of NSCLC cells. It also shows the synergistic effects of isothiocyanates in combination with gefitinib for treating NSCLC cells (32).

Indole-3-carbinol

It has been shown that the superiority of the anti-tumor impact of indole-3-carbinol in comparison with N-acetylcysteine through an increase in antioxidant and viability activity and activating apoptotic signaling cascades against human lung cancer H1299 cells. Additionally, the expression of anti-apoptotic proteins such as thioredoxin1 and peroxiredoxin-1 was decreased in indole-3-carbinol -treated cells, meanwhile the expression of pro-apoptotic proteins such as active MAP3K5 (mitogen-activated protein kinase 5) were increased in comparison with cells co-treated with N-acetylcysteine (33).

Genistein

Genistein is a natural isoflavone that has been studied as an effective anti-cancerous substance in various types of lung cancer (34). Several studies suggest that this compound has the potential to inhibit the growth of NSCLC cells without harming normal human lung cells, making it an attractive therapeutic option for those affected by this common form of cancer (35). It has also been shown to induce cell cycle arrest and promote apoptosis in NSCLC cells, and to prevent metastasis and encourage tumor cell colonization in their site by upregulating vasodilator-simulated phosphoprotein (36). In addition, Yang et al showed that genistein prevents A549 human lung cancer cell proliferation associated with miR-27a-mediated MET signaling; they also showed an association between the anti-malignancy efficacy of genistein with miR-27a-mediated MET signaling (28). It seems that, this study is a pilot investigation to detect the molecular basis of genistein in cancer, which requires further studies (34,35).

Curcumin

Curcumin is a nontoxic natural product with preventive effects on multiple pathways for carcinogenesis. Curcumin may be the best adjunctive therapy for lung cancer because of its nontoxicity, broad-reaching mechanism of action, and anticancer effects. However, more evidence and further clinical studies are required (37,38).

Fisetin

Different assays confirmed that fisetin inhibited migration, adhesion, proliferation and invasion and induced apoptosis in the A549 cell line via targeting the extracellular signal-regulated kinase-signaling pathway (39,40).

Pomegranate polyphenols

The effect of pomegranate leaf extracts, such as punicalagin and ellagic acid, on a lung carcinoma cell line, has been investigated. It was observed that treatment with leaf extracts caused a significant reduction of tumor cell proliferation and induced the apoptotic process. In addition, the ability of extracts to weaken the migration/invasion of tumor cells is proven by the decrease in the levels of MMP-2 and MMP-9. It is supposed that the non-eatable portions of pomegranate may show a new adjuvant for cancer treatment (41,42).

Luteolin

It has been shown that luteolin prevents migration and invasion of pulmonary malignant cells via intracellular tyrosine kinases, namely FAK (focal adhesion kinase), SRC-3 (steroid receptor coactivator-3), and its downstream pathways such as RAC1 (ras-related C3 botulinum toxin substrate 1). Luteolin might be a good choice for withholding invasion and metastasis of lung cancer cells (43).

Resveratrol

A review summarized current in vitro and in vivo studies on resveratrol and its anti-lung cancer properties (44). It found that resveratrol prevents cancer cell proliferation and induces apoptosis and cell cycle arrest via modulation of signaling molecules involved in these processes.

Conclusion

Plants are detected as one of the attractive approaches for pulmonary malignancy since they have established to be effective in sensitizing conventional chemotherapy agents, prolonging individuals' survival time, preventing adverse reactions of chemotherapy, promoting physiological improvement and improving quality of life in lung cancer patients. The natural product molecules with anticancer activities have the molecular mechanisms for developing anti-malignancy therapies, including inducing apoptosis, inhibiting angiogenesis and metastasis, reversing multidrug resistance, and targeting reactive oxygen species signaling.

Authors' contribution

Conceptualization: AT, MK and RT.
Validation: AT, MK and RT.
Formal analysis: AP.
Investigation: SY, PS, MS and PM.
Resources: MK.
Data curation: AT, RT and MK.
Writing—original draft preparation: MK, AT, AP and RT.

Writing—reviewing and editing: MS, PM, SY, PS, AT, AP, ZGH and RT.
Visualization: MK and AT.
Supervision: MK and AT.
Project management: AT, RT and MK.
Funding acquisition: MK.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

References

1. Hodgson JT, Darnton A. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Annals of Occupational Hygiene. 2000;44:565-601.
2. Rom WN, Hay JG, Lee TC, Jiang Y, Tchou-Wong KM. Molecular and genetic aspects of lung cancer. Am J Respir Crit Care Med. 2000;161:1355-67. doi: 10.1164/ajrccm.161.4.9908012.
3. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2013;143:e1S-e29S. doi: 10.1378/chest.12-2345.
4. Surien O, Ghazali AR, Masre SF. Lung cancers and the roles of natural compounds as potential chemotherapeutic and chemopreventive agents. Biomed Pharmacol J. 2019;12:85-98. doi:10.13005/bpj/1617.
5. Jeong S-J, Koh W, Kim B, Kim S-H, Are there new therapeutic options for treating lung cancer based on herbal medicines and their metabolites? J Ethnopharmacol. 2011;138:652-61. doi: 10.1016/j.jep.2011.10.018.
6. Dan W, Liu J, Guo X, Zhang B, Qu Y, He Q. Study on medication rules of modern chinese herbal medicine in the treatment of non-small cell lung cancer based on data mining. Evid Based Complement Alternat Med. 2020;2020:7498525. doi: 10.1155/2020/7498525.
7. Zhong W-l, Qin Y, Chen S, Sun T. Antitumor Effect of natural product molecules against lung cancer. In: Adonis M, ed. A Global Scientific Vision - Prevention, Diagnosis, and Treatment of Lung Cancer. IntechOpen; 2017. p. 201-220. doi: 10.5772/67241.
8. Sarwar MS, Zhang H-J, Tsang SW. Perspectives of plant natural products in inhibition of cancer invasion and metastasis by regulating multiple signaling pathways. Curr Med Chem. 2018;25:5057-87. doi: 10.2174/0929867324666170918123413.
9. Chanvorachote P, Chamni S, Ninsontia C, Phiboonchaiyanan PP. Potential anti-metastasis natural compounds for lung cancer. Anticancer Res. 2016;36:5707-5717. doi: 10.21873/anticanres.11154.
10. Hipfner DR, Mao Q, Qiu W, Leslie EM, Gao M, Deeley RG, et al. Monoclonal antibodies that inhibit the transport function of the 190-kDa multidrug resistance protein, MRP. Localization of their epitopes to the nucleotidebinding dins of the protein. J Biol Chem. 1999;274:15420-6.
11. Einhorn LH. First-line chemotherapy for non-small-cell lung cancer: is there a superior regimen based on histology? J Clin Oncol. 2008;26:3485-6. doi: 10.1200/JCO.2008.17.2056.
12. Lee Y-M, Lee G, Oh T-I, Kim BM, Shim D-W, Lee K-H, et al. Inhibition of glutamine utilization sensitizes lung cancer cells to apigenin-induced apoptosis resulting from metabolic and oxidative stress. Int J Oncol. 2016;48:399-408. doi: 10.3892/ijo.2015.3243.
13. Zhai T, Li S, Hu W, Li D, Leng S. Potential Micronutrients and Phytochemicals against the Pathogenesis of Chronic Obstructive Pulmonary Disease and Lung Cancer. Nutrients. 2018;10:813. doi: 10.3390/nu10070813.
14. Kim Y, Lian F, Yeum KJ, Chongviriyaphan N, Choi SW, Russell RM, et al. The effects of combined antioxidant (beta-carotene, alpha-tocopherol and ascorbic acid) supplementation on antioxidant capacity, DNA single-strand breaks and levels of insulin-like growth factor-1/IGF-binding protein 3 in the ferret model of lung cancer. Int J Cancer. 2007;120:1847-54. doi: 10.1002/ijc.22320.
15. Amararathna M, Johnston MR, Rupasinghe HP. Plant Polyphenols as Chemopreventive Agents for Lung Cancer. Int J Mol Sci. 2016;17:1352. doi: 10.3390/ijms17081352.
16. Oghumu S, Casto BC, Ahn-Jarvis J, Weghorst LC, Maloney J, Geuy P, et al. Inhibition of pro-inflammatory and anti-apoptotic biomarkers during experimental oral cancer chemoprevention by dietary black raspberries. Front Immunol. 2017;8:1325. doi: 10.3389/fimmu.2017.01325.
17. Montes de Oca MK, Pearlman RL, McClees SF, Strickland R, Afaq F. Phytochemicals for the prevention of photocarcinogenesis. Photochem Photobiol. 2017;93:956-74. doi: 10.1111/php.12711.
18. Kwon CY, Lee B, Kong M, Lee SH, Jung HJ, Kim KI, Lee BJ. Effectiveness and safety of herbal medicine for cancer-related fatigue in lung cancer survivors: A systematic review and meta-analysis. Phytother Res. 2021;35:751-70. doi: 10.1002/ptr.6860.
19. Greenberg AK, Tsay JC, Tchou-Wong KM, Jorgensen A, Rom WN. Chemoprevention of lung cancer: prospects and disappointments in human clinical trials. Cancers (Basel). 2013;5:131-48. doi: 10.3390/cancers5010131.
20. Lemjabbar-Alaoui H, Hassan OU, Yang YW, Buchanan P. Lung cancer: biology and treatment options. Biochim Biophys Acta. 2015;1856:189-210. doi: 10.1016/j.bbcan.2015.08.002.
21. Singh J, Luqman S, Meena A. Emerging role of phytochemicals in targeting predictive, prognostic, and diagnostic biomarkers of lung cancer. Food Chem Toxicol. 2020;144:111592. doi: 10.1016/j.fct.2020.111592.
22. Monteiro Lde S, Bastos KX, Barbosa-Filho JM, de Athayde-Filho PF, Diniz Mde F, Sobral MV. Medicinal plants and other living organisms with antitumor potential against lung cancer. Evid Based Complement Alternat Med. 2014;2014:604152. doi: 10.1155/2014/604152.
23. 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.
24. Shin JA, Shim JH, Jeon JG, Choi KH, Choi ES, Cho NP, et al. Apoptotic effect of *Polygonum cuspidatum* in oral cancer cells through the regulation of specificity protein 1. Oral Dis. 2011;17:162-70. doi: 10.1111/j.1601-0825.2010.01710.x.
25. Yang CJ, Huang YJ, Wang CY, Wang CS, Wang PH, Hung JY, et al. Antiproliferative and antitumorigenic activity of *Toona sinensis* leaf extracts in lung adenocarcinoma. J Med Food. 2010;13:54-61. doi: 10.1089/jmf.2009.1166.
26. 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.
27. Hsu YL, Kuo PL, Liu CF, Lin CC. Acacetin-induced cell cycle arrest and apoptosis in human non-small cell lung cancer A549 cells. Cancer Lett. 2004;212:53-60. doi: 10.1016/j.canlet.2004.02.019.

28. Yang SF, Chu SC, Liu SJ, Chen YC, Chang YZ, Hsieh YS. Antimetastatic activities of *Selaginella tamariscina* (Beauv.) on lung cancer cells in vitro and in vivo. J Ethnopharmacol. 2007;110:483-9. doi: 10.1016/j.jep.2006.10.010.
29. Liang CH, Shiu LY, Chang LC, Sheu HM, Tsai EM, Kuo KW. Solamargine enhances HER2 expression and increases the susceptibility of human lung cancer H661 and H69 cells to trastuzumab and epirubicin. Chem Res Toxicol. 2008;21:393-9. doi: 10.1021/tx700310x.
30. Heng WS, Kruyt FAE, Cheah SC. Understanding lung carcinogenesis from a morphostatic perspective: prevention and therapeutic potential of phytochemicals for targeting cancer stem cells. Int J Mol Sci. 2021;22:5697. doi: 10.3390/ijms22115697.
31. Khan N, Mukhtar H. Dietary agents for prevention and treatment of lung cancer. Cancer Lett. 2015;359:155-64. doi: 10.1016/j.canlet.2015.01.038.
32. Zhang Q, Chen M, Cao L, Ren Y, Guo X, Wu X, et al. Phenethyl isothiocyanate synergistically induces apoptosis with Gefitinib in non-small cell lung cancer cells via endoplasmic reticulum stress-mediated degradation of Mcl-1. Mol Carcinog. 2020;59:590-603. doi: 10.1002/mc.23184.
33. Lim HM, Park SH, Nam MJ. Induction of apoptosis in indole-3-carbinol-treated lung cancer H1299 cells via ROS level elevation. Hum Exp Toxicol. 2021;40:812-825. doi: 10.1177/0960327120969968.
34. Yu Y, Xing Y, Zhang Q, Zhang Q, Huang S, Li X, Gao C. Soy isoflavone genistein inhibits has_circ_0031250/miR-873-5p/FOXM1 axis to suppress non-small-cell lung cancer progression. IUMB Life. 2020;73:107-92. doi: 10.1002/iub.2404.
35. Nimmano N, Somavarapu S, Taylor KMG. Aerosol characterisation of nebulised liposomes co-loaded with erlotinib and genistein using an abbreviated cascade impactor method. Int J Pharm. 2018;542:8-17. doi: 10.1016/j.ijpharm.2018.02.035.
36. Zhu Y, Xie N, Chai Y, Nie Y, Liu K, Liu Y, et al. Apoptosis induction, a sharp edge of berberine to exert anti-cancer effects, focus on breast, lung, and liver cancer. Front Pharmacol. 2022;13:803717. doi: 10.3389/fphar.2022.803717.
37. Wang M, Jiang S, Zhou L, Yu F, Ding H, Li P, et al. Potential mechanisms of action of curcumin for cancer prevention: focus on cellular signaling pathways and miRNAs. Int J Biol Sci. 2019;15:1200-14. doi: 10.7150/ijbs.33710.
38. Liu Z, Huang P, Law S, Tian H, Leung W, Xu C. Preventive effect of curcumin against chemotherapy-induced side-effects. Front Pharmacol. 2018;9:1374. doi: 10.3389/fphar.2018.01374.
39. Wang J, Huang S. Fisetin inhibits the growth and migration in the A549 human lung cancer cell line via the ERK1/2 pathway. Exp Ther Med. 2018;15:2667-2673. doi: 10.3892/etm.2017.5666.
40. Liao YC, Shih YW, Chao CH, Lee XY, Chiang TA. Involvement of the ERK signaling pathway in fisetin reduces invasion and migration in the human lung cancer cell line A549. J Agric Food Chem. 2009;57:8933-41. doi: 10.1021/jf902630w.
41. Turrini E, Ferruzzi L, Fimognari C. Potential effects of pomegranate polyphenols in cancer prevention and therapy. Oxid Med Cell Longev. 2015;2015:938475. doi: 10.1155/2015/938475.
42. Hussein AM, El-Beih NM, Swellam M, El-Hussieny EA. Pomegranate juice and punicalagin-mediated chemoprevention of hepatocellular carcinogenesis via regulating miR-21 and NF-κB-p65 in a rat model. Cancer Cell Int. 2022;22:333. doi: 10.1186/s12935-022-02759-9.
43. Masraksa W, Tanasawet S, Hutamekalin P, Wongtawatchai T, Sukketsiri W. Luteolin attenuates migration and invasion of lung cancer cells via suppressing focal adhesion kinase and non-receptor tyrosine kinase signaling pathway. Nutr Res Pract. 2020;14:127-133. doi: 10.4162/nrp.2020.14.2.127.
44. Yousef M, Vlachogiannis IA, Tsiani E. Effects of resveratrol against lung cancer: in vitro and in vivo studies. Nutrients. 2017;9:1231. doi: 10.3390/nu9111231.