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Phytochemicals Potential to treat lung cancer: A Review

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ABSTRACT

Lung cancer remains one of the most prevalent and deadly malignancies worldwide, necessitating the development of more effective and less toxic therapeutic strategies. Phytochemicals-bioactive compounds derived from plants have garnered significant attention for their potential anticancer properties. This review highlights the phytochemical constitution of various medicinal plants and their mechanistic roles in combating lung cancer. Key classes of phytochemicals, such as flavonoids, alkaloids, terpenoids and phenolic acids, demonstrate anticancer effects through multiple pathways, including the induction of apoptosis, inhibition of cell proliferation, suppression of angiogenesis, and modulation of signaling pathways like PI3K/Akt, MAPK, and NF-κB. Compounds such as curcumin, resveratrol, quercetin and epigallocatechin gallate (EGCG) have shown promising results in preclinical and clinical settings. Moreover, phytochemicals may enhance the efficacy of conventional chemotherapeutics while reducing their side effects. This review highlights the potential of plant-derived compounds as complementary or alternative therapeutic agents for lung cancer and encourages further research into their clinical applicability and molecular mechanisms.

Key words: Angiogenesis, anticancer, lung cancer, phytochemicals, signaling pathways

1. INTRODUCTION

On a global scale, lung cancer is the second most prevalent form of the disease. Over the last four decades, its death rate was 59.0 per 100,000 person-years. In the year 2020, lung cancer was the major cause of death from cancer, accounting for roughly one in ten (11.4 %) malignancies diagnosed and one in five (18.0 %) fatalities (35). While this was going on, the survival rate after five years was lower than 21 % (22). On a daily basis, around 350 people in the United States passed away from lung cancer in 2022 (2). Among males in China, lung cancer is the most prevalent form of the disease (50.04 per 100,000), whereas it is the second most prevalent form among females (23.6 per 100,000) (34). When normal epithelial lung cells undergo repeated cell mutations, they eventually transform into uncontrolled proliferating cells that undergo degenerative alterations and pose a hazard to the pulmonary airway (3). This is the process that leads to the development of lung cancer.

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The study of the possible chemicals found in plants, aquatic creatures, microbes, and animals, as well as the synthesis of lead compounds taken from natural products, led to the discovery of a few chemotherapeutic drugs that are routinely administered (27). Numerous studies have demonstrated that natural dietary products, such as grapes, pomegranates, apples, cruciferous vegetables, tomatoes, bitter melons, turmeric, ginger, saffron, garlic, chili, rosemary, soy, rice bran, corn, shiitake mushroom, *Calvatia gigantea*, and *Thelephora ganbajun* act as an essential part in the treatment and control of Lung Cancer (shown in Figure 1)**.** These consumable natural products and their bioactive components affect cancer development and progression through various mechanisms, including the suppression of cancer cell growth and proliferation, the induction of cell apoptosis, protection against lung carcinogens, inhibition of cell migration and adhesion, and immunomodulation that sensitises cancer cells to antitumor agents (5, 24). Recent research, particularly in 2023–2025, has increasingly focused on overcoming the traditional limitations of phytochemical therapy, such as poor bioavailability and metabolic instability, through novel delivery systems including nanocarriers, liposomes, and phytosome formulations. Moreover, emerging preclinical and clinical studies suggest that phytochemicals can synergize with existing chemotherapeutics to enhance efficacy and reduce toxicity, especially in non-small cell lung cancer (NSCLC), the most prevalent subtype. In addition, the application of network pharmacology, transcriptomic analysis and AI-assisted drug discovery is accelerating the identification of phytochemical targets and mechanisms, supporting their integration into precision medicine (28). The purpose of this study is to present a comprehensive account of several phytochemicals that have been demonstrated to play an important role in the fight against lung cancer, in conjunction with chemotherapeutic drugs.

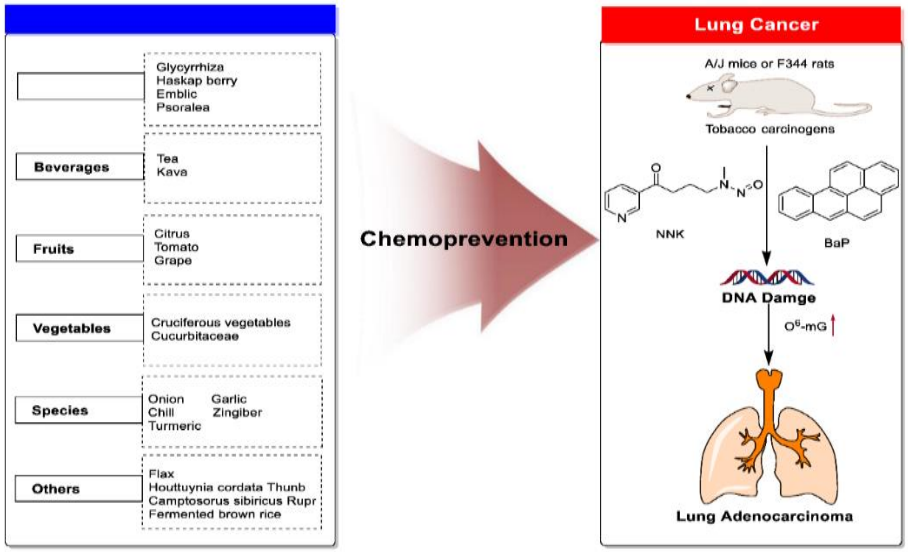

Figure 1. Graphic summary of dietary phytochemicals that are cancer-preventive on BaP or NNK triggered lung carcinogenesis.

2. NATURAL PRODUCTS IN CANCER TREATMENT

Natural products, derived from plants, microbes, and marine organisms, have historically played a critical role in the discovery and development of anticancer drugs. Many chemotherapeutic agents, such as paclitaxel, vinblastine and camptothecin, were originally derived from natural sources (26). Natural products have been used as medicine and remedies since ancient times to treat many ailments worldwide. Such instances have been recorded in various scriptures, such as the first treatise named Charaka Samhita that recorded the concepts of Indian Ayurveda; Chinese medical book, Wu Shi Er Bing Fang which recorded more than 200 natural products along with drug formulation; and Ben Cao Gang Mu recorded with more than 1000 natural agents and published back in 16th century. The bioactive compounds in natural products (Figure 2) can interfere with cancer cell proliferation, induce apoptosis, inhibit metastasis, and modulate immune responses, making them promising candidates for lung cancer treatment. Natural products have shown significant potential in lung cancer treatment due to their ability to interfere with cancer cell growth, induce apoptosis (cell death), and reduce the side effects of conventional therapies. Here's an overview of natural products in lung cancer treatment (1).

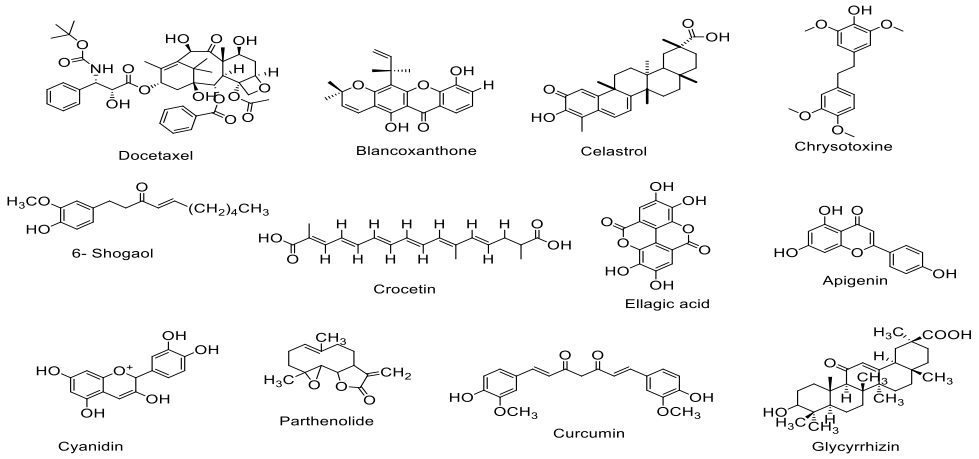

Figure 2- Chemical representation of natural compounds studied for lung diseases

Lidia-Ioana Virchea *et al.* (20) reported that the *Achillea millefolium* L. (yarrow), a medicinal herb from the Asteraceae family, is rich in phenolic compounds and volatile oils with antioxidant, anti-inflammatory, and antimicrobial properties. Traditionally used for various ailments, its extracts-both pure and nanoparticle-incorporated-have been studied for cytotoxic effects against small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC) and normal cell lines, highlighting its potential in lung cancer treatment (20).

Anuj Singh *et al.* (35) concluded by their study that *Moringa oleifera*, a plant rich in bioactive compounds, showed a promising effect in lung cancer treatment. Its natural compounds, such as quercetin, kaempferol and niazimicin, have been found to target various molecular pathways involved in lung cancer progression. Potential targets for these

compounds include PI3K/AKT, MAPK/ERK, and NF-κB signaling pathways, which regulate cell proliferation, apoptosis, and metastasis. Quercetin, for instance, has been shown to inhibit lung cancer cell growth and induce apoptosis by modulating these pathways. Kaempferol has also demonstrated anti-proliferative and anti-metastatic effects by suppressing the expression of matrix metalloproteinases. These natural compounds may offer a promising approach to lung cancer treatment, potentially reducing the side effects associated with conventional chemotherapy (35).

Deng *et al.* (12) in their study reported that Glycyrrhizin (GA) is the major bioactive component found in liquorice roots of a small leguminous shrub, *Glycyrrhiza glabra L.* In athymic BALB/c nude mice xenograft with human lung adenocarcinoma A549 cells stably transfected with TxA2 receptor (TPa), GA (135 mg/kg) reduced thromboxane synthase (TxAS) and proliferating cell nuclear antigen (PCNA) expression via suppressing TxA2 pathway**.** More recent findings showed that GA (100 mg/kg) inhibited the growth of non-small cell lung cancer cells (NSCLC) in patient-derived xenograft (PDX) mice by suppressing the level of high mobility group box 1 (HMGB1) and inhibition of JAK/STAT signaling pathway (12).

Kotsakis *et al.* (22) reviewed that taxanes represent promising anticancer drugs that were first isolated from the bark of the Yew tree. Taxanes exert an anticancer effect by stabilizing microtubules, resulting in cell cycle arrest and aberrant mitosis. Paclitaxel, a natural product isolated from the bark and leaf of Taxus brevifolia, and docetaxel, a semi-synthetic derivative, are primarily used in breast, ovarian, pancreatic, prostate, and lung cancer therapies (22).

Zhang *et al.* (18) showed by their study that cyanidin belongs to the anthocyanins, a subclass of flavonoids found in cranberries, concord grapes, pomegranates and bilberries, just to name a few fruits. Anthocyanins are the pigments that give red, purple and blue plants their rich colouring. In addition to acting as antioxidants and fighting free radicals, anthocyanins may offer anti-inflammatory, anti-viral, and anti-cancer benefits (18).

Treesuppharat *et al*. (39) carried out an anti-cancer potential and oral toxicity study of anthraquinone (damnacanthal) extracted from the roots of *Morinda citrifolia*. The result of the study showed that damnacanthal inhibits the growth of human colorectal cancer cells in a dose-dependent and time-dependent manner. In the oral treatment of damnacanthal, the growth of the colorectal tumor xenografts in nude mice was found to be 2-3 times higher when compared to standard drug 5- 5-fluorouracil. The results revealed the potential therapeutic activity of the natural damnacanthal compound as an anti-colorectal cancer drug (39).

Kim *et al.* (19) isolated 6-Shogaol a minor, bioactive component from ginger (*Zingiber officinale*, Roscoe). In a nude mice model of non-small cell lung cancer (NSCLC), 6-shogaol (10 mg/kg) significantly inhibited the growth of NCI-H1650 lung cancer cells which was associated with decreased cell proliferation and increased apoptosis as evidenced by reduced Ki-67-positive cells and an increased number of terminal deoxynucleotidyl transferase deoxyuridine triphosphate nick-end labelling (TUNEL)-positive cells. At the in vitro level, 6-shogaol suppressed Akt signaling through direct targeting of Akt1 and Akt2 (19).

Moreover, Li *et al.* (34) have reported that Parthenolide is a sesquiterpenoid found in the plant feverfew (*Tanacetum parthenium*). The highest concentrations are found in flowers and fruits. It has been reported to inhibit human lung cancer cell growth by modulating the IGF-1R/PI3K/AKT signalling pathway. Demonstrated that parthenolide inhibits proliferation of papillary thyroid carcinoma cells in vitro and mouse tumour xenografts by down-regulating the mTOR/PI3K/AKT signalling pathway (34).

Wang *et al.* (37) have reported that curcumin inhibits migration and invasion of non-small cell lung cancer cells through up-regulation of miR.206 and suppression of PI3K/AKT/mTOR signalling axis. Finally, curcumin has also been shown to down-regulate the PI3K/AKT/mTOR pathway and inhibit the growth and progression of head and neck cancer cells (37).

Bufu *et al.* (5) reported that Celastrol is a triterpene compound derived from TCM. It was isolated from root extracts of *Tripterygium wilfordii* and reported to possess potential anti-tumour activity. Their study showed that celastrol inhibits colorectal cancer cell proliferation and migration through suppression of matrix metalloproteinases 3 (MMP3) and 7 (MMP7) by the PI3K/AKT signalling pathway. Celastrol inhibits colon cancer cell proliferation by down-regulating miR-21 and PI3K/AKT/GSK-3 beta pathway (5).

Ayushi *et al.* (32) extracted and isolated the flavonoid content of *Camellia sinensis*. The flavonol quercetin obtained from *Camellia sinensis* was subjected to the estimation of anticancer activity. Anticancer ability was determined on the ovarian cancer cell line by *in vitro* method. The results depicted that the flavonoids, especially quercetin, work as a good antineoplastic agent. The outcomes revealed that naturally available anticancer agents having good potential and lesser toxicity can be obtained from easily available natural sources like green tea leaves (32).

2.1. Phytochemicals Related Patents for Lung Cancer

Several patents have been filed focusing on the use of phytochemicals for lung cancer treatment as under:

(i). Title- Composition of Eleven Herbals for Treating Cancer

Patent Number: US6780441B2

Summary: This patent describes a pharmaceutical preparation comprising a mixture of eleven herbs, including *Withania somnifera*, *Chlorophytum borivilianum*, and *Boerhavia diffusa*. The formulation has been found effective in treating lung cancer, particularly bronchogenic carcinomas and pleural malignancies.

(ii). Title- Synergistic Pharmaceutical Composition for Lung Cancer Treatment

Patent Number: US9622987B2

Summary: This patent covers a composition derived from the seeds of Litsea cubeba. The volatile compounds from the extracted oil induce apoptosis and prevent proliferation of non-small cell lung cancer (NSCLC) cells by deactivating the Akt pathway.

(iii). Title- Cephalotaxus Extract for Preventing or Treating Lung Cancer

Patent Application Number: US20240058405A1

Summary: This application discusses a pharmaceutical composition containing compounds isolated from *Cephalotaxus* species, such as isoharringtonine and homoharringtonine. These compounds are noted for their potential in preventing or treating lung cancer, including forms resistant to EGFR-TKIs

Table 1. Patent list of phytochemical plants in lung cancer

S. No	Plant Name	Patent Title	Patent No.	Approval Date	Country	Ref
1	Capilliposide	Preparation method and application of lysimachia capillipes saponin A	CN105037483A	2015-11-11	China	21
2	Daidzein	A forage growth promoter and application of daidzein, genistein, or palmitic acid in promoting forage growth	CN116602300B	2025-02-11	China	16
3	Embelia ribes	Methods of treating inner ear fibrosis	WO2025032553A1	2025-02-13	WIPO (PCT)	10
4	6-Gingerol	Compositions and methods to treat cancer and diseases and conditions responsive to cell growth inhibition	US9632074B2	2017-04-25	USA	8
5	Tetrahydro-cannabinol	Manufacture methods, compositions and medical applications of orally administered cannabis pharmaceuticals	CA3022553C	2023-02-21	Canada	23
6	Kaempferol	Anti-biofilm compositions and methods for using	US20120088671A1	2014-06-03	USA	9
7	Kaempferol, Galactoside	Preparations containing berry extracts for treatment of viral infections caused by pneumoviridae	WO2020201055A1	2020-10-08	WIPO (PCT)	15
8	Phloretin	Compositions for elimination of senescent cells	AU2019365405B2	2024-12-12	Australia	17
9	Solamargine	Application of solamargine to prepare anti-tumor drug sensitizer and an anti-tumor combined drug	CN111870614A	2020-11-03	China	33
10.	Tanshinone I	A synchronous green extraction method for salvianolic acid B, tanshinone I, cryptotanshinone and tanshinone IIA in Salvia miltiorrhiza	CN119118970A	2024-12-13	China	40

(iv). Title- Natural Plant Essential Oils in Cancer Treatment

Patent Number: US7291650B2

Summary: This patent presents compositions and methods utilizing natural plant essential oils for cancer treatment. The essential oils are noted for their potential in inhibiting cancer cell growth and metastasis.

(v). Title- Composition for Treatment or Prevention of Lung Cancer

Patent Application Number: US20190060384A1

Summary: This application details a method for treating or preventing lung cancer using a composition comprising gefitinib and *Lonicera japonica* extract. The combination aims to enhance treatment efficacy and reduce side effects associated with lung cancer therapies. Table 1 represents some other notable examples.

Some other phytochemicals are also reported to be as an intervention to manage lung cancer (Table 2).

Table 2. Plant-Based Phytochemicals for lung cancer

S. No	Plant name	Phytochemical	Activity	Category	Ref
1.	*Curcuma longa*	Curcuminoids	Anticancer, Antimicrobial	Zingiberaceae	6
2.	*Camellia sinensis*	Alkaloid, saponin, steroid/ Triterpenoid, Flavonoid	Neuroprotective, Anticancer	Theaceae	37
3.	*Cinnamomum camphora*	Safrole, Linalool, 1,8-Cineole	Antipyretic	Terpenoids	32
4.	*Glycyrrhiza glabra* (Licorice Plant)	Glycyrrhizin	Anti-inflammatory	Triterpenoid Saponins	11
5.	*Morinda citrifolia*	Damnacanthal	Anticancer, Anti-inflammatory	Alkaloid	38
6.	*Piper methysticum*	Dihydromethysticin, yangonin	Antianxiety	Piperaceae	13
7.	*Phyllanthus emblica L.*	Phyllanthin and Emblicanintannins, polyphenols, gallic acid, flavonoids and vitamin C.	Anti-diabetic, Antioxidant	Phyllanthaceae.	14
8.	*Psoralea corylifolia*	flavones, monoterpenes, chalcones, lipids, resins,	Antioxidant, Antitumor	Fabaceae	29
9.	*Psoralea coryli*folia (Babchi)	Psoralen and Isopsoralen, Bakuchiol	Antiviral, Antioxidant, antitumor	Fabaceae	4
10.	Vinca	Vindoline, Catharanthine,	Antitumor	alkaloid	2

3. LIMITATIONS IN DISCOVERY OF PHYTOCHEMICALS

The discovery of phytochemicals for anticancer drugs is a promising area of research, but it is hindered by several limitations. One significant challenge is the complexity of plant extracts, which often contain multiple phytochemicals, making it difficult to identify the specific compound responsible for anticancer activity. Furthermore, the process of isolating and purifying individual phytochemicals can be time-consuming and costly, which can slow down the discovery process. Additionally, the limited understanding of the molecular mechanisms underlying the anticancer activity of phytochemicals can make it challenging to design effective clinical trials. Regulatory and safety concerns also pose significant limitations, as phytochemicals can have potential side effects and interact with other medications. Moreover, the scalability and commercialization of phytochemical-containing anticancer drugs can be limited by factors such as standardization, quality control, and market demand. These limitations highlight the need for continued research and development to overcome the challenges associated with discovering and developing phytochemical-containing anticancer drugs.

4. FUTURE PERSPECTIVE: NATURAL PRODUCTS

Natural products have long been a cornerstone in the development of therapeutic agents, and their role in combating lung cancer is both promising and multifaceted. Lung cancer, being one of the leading causes of cancer-related deaths worldwide, necessitates innovative approaches for treatment and prevention. Natural products, derived from plants, microorganisms, and marine organisms, offer a reservoir of bioactive compounds with potential anticancer properties**.** It has demonstrated efficacy in targeting various pathways involved in lung cancer progression. For instance, compounds like paclitaxel and vinorelbine, derived from natural sources, are already in clinical use for treating lung cancer. These compounds work by disrupting microtubule dynamics, thereby inhibiting cancer cell proliferation. Additionally, flavonoids, alkaloids, and terpenoids have shown promise in preclinical studies for their ability to induce apoptosis, inhibit angiogenesis, and suppress metastasis in lung cancer cells.

5. CONCLUSIONS

Phytochemicals, naturally occurring compounds in plants, have shown promising potential in combating lung cancer. These bioactive molecules, such as flavonoids, alkaloids, and terpenoids, exhibit anti-cancer properties by targeting multiple pathways involved in carcinogenesis. They act as antioxidants, inhibit tumor proliferation, induce apoptosis, and modulate immune responses. Phytochemicals like curcumin, resveratrol and quercetin have been extensively studied for their ability to suppress lung cancer progression while minimizing side effects compared to conventional therapies.

Recent advancements in nanotechnology have enhanced the delivery of phytochemicals, ensuring better bioavailability and targeted action. This synergy between phytochemicals and modern drug delivery systems offers a promising avenue for lung cancer treatment. However, further research and clinical trials are essential to fully harness their therapeutic potential. By integrating phytochemicals into cancer treatment regimens, we can move towards safer and more effective solutions for managing lung cancer**.**

DECLARATION

We declare that all authors of this manuscript have made substantial contributions. We did not exclude any author who substantially contributed to this manuscript. We have followed the ethical norms established by our respective institutions.

AUTHORS CONTRIBUTION

RKM conceived of the present idea for the article. ASM, AJR performed the literature search and data analysis and wrote the manuscript. RPM provided critical feedback and helped to shape the final draft.

CONFLICT OF INTEREST

The authors announce that they have no conflict of interest.

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ETHICAL APPROVAL

The authors declare that the study was carried out following scientific ethics and conduct. However, this study did not involve any use of animals, hence no ethical approval has been obtained from the concerned committee.

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