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Phytopharmacological Communications
DOI: doi.org/10.55627/ppc.004.001.0546

Review Article

Phytocompounds as Promising Weapons against Lung Cancer: A Review

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Abstract

Lung cancer is the second most prevalent form of cancer in both men and women, which incurs major economic and public health losses. Notably, easy access to tobacco is the most important cause of pulmonary cancer, with 80%–90% of cases coming from cigarette smokers. Moreover, respiratory issues caused by industrial and automobile smoke, occupational hazards like asbestos, and infections, like Covid-19, exacerbate the impact of lung cancer on the body. To mitigate these effects, traditional lung cancer treatments coupled with awareness campaigns are proving somewhat successful, but many challenges persist. Cancer-resistance development, chemotherapy-induced side effects, and cancer metastasis are some of the significant hurdles to lung chemotherapy success. Plant and phytocompounds can potentially become alternative sources of lung cancer treatments. This review article provides some insight into these natural sources. Particular, hispidulin from *Saussurea involucrate,* erianin from *Dendrobium chrysotoxum,* and albanol B from *Morus alba* are proven to have anti-cancer effects in lung cancer cells, proven through *in vitro* and *in vivo* animal models. Furthermore, petroleum ether and ethyl acetate extracts of *Marsdenia tenacissima* were found to be potent in inhibiting lung cancer cells with an IC_{50} value of 0.35 mg/ml. This makes *M. tenacissima* a suitable candidate for further exploration in lung cancer treatment. In addition to the therapeutic effects, plant-based products can also act as dietary supplements for cancer prevention, and may even be recommended for cancer patients. The possibilities are endless but require further research and resource investment for estimating the clinical efficacy, as well as robust drug-delivery mechanisms of these plants and phytocompounds for pulmonic cancer.

Keywords: Lung cancer, phytocompound, plants-based chemotherapy, anti-cancer, herbal remedies

1. Introduction

In 2021, lung cancer was among the leading causes of global cancer incidence and mortality, accounting for an estimated 2 million diagnoses and 1.8 million deaths. Following prostate cancer in men and breast cancer in women, neoplasm of the lung is the second most common cancer diagnosis (Chaitanya Thandra et al. 2021). From the indiscriminate and easy access to tobacco, and occupational hazards like asbestos, to toxic fumes spewed out by the contraptions of the industrialized world, there are many socioeconomic factors involved in the meteoric rise of lung cancer diagnosis; notably, lung cancer is more prevalent in economically developed countries. However, in low-income and middle-income countries at the later stages of the tobacco epidemic, both lung cancer incidence and mortality are exhibiting an upward trend (Leiter, Veluswamy, and Wisnivesky 2023). Through a systemic review, the authors uncovered an alarming trend, while younger men are experiencing a decline, there is a concerning rise in lung cancer rates among younger women, even though these women are not smoking more than their male counterparts (Fidler-Benaoudia et al.

2020). There could be many factors involved behind the increased prevalence of pulmonary cancer in women, like biological differences as female smokers tend to have higher levels of DNA damage from tobacco carcinogens compared to males (Mollerup et al. 1999). In addition, genetic mutations in tumor suppression p53 and K-RAS proto-oncogenes are more common in females with lung cancer. Moreover, the interaction between smoking and sex hormones (estrogen) might play a role. For instance, a higher lung cancer rate was recorded in women using hormone replacement therapy (HRT) or birth control pills. Similarly, more pre-menopausal women were diagnosed compared to men or post-menopausal women (Stapelfeld, Dammann, and Maser 2020). A study where men given estrogen for heart health showed increased lung cancer risk (Group 1973) In addition to the lethal aftermath of lung cancer diagnosis, the stigma attached to this disease makes the treatment and care even more challenging (Hamann et al. 2021).

Non-small cell lung cancer (NSCLC) comprises approximately 85% of lung cancer cases and includes all types of epithelial lung cancer except small cell lung cancer (SCLC). The main subtypes of NSCLC are squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma (Xing, Hu, and Wang 2022). Furthermore, racial and familial factors also increase one's predisposition to lung cancer (Chaitanya Thandra et al. 2021). There are many challenges associated with lung cancer treatment, spanning from tumor microenvironment to access to affordable chemotherapy. Due to huge human capital losses incurred by lung cancer, there is an increasing interest in the prevention, early detection with screening, and development of new treatments.

2. Lung Cancer Pathophysiology

Lung cancer pathophysiology is a relatively unclear and complex phenomenon. There are numerous factors are involved in the progression of lung cancer such as inflammation, oxidative stress, mitochondrial dysfunction, and abnormal releases of hormones and enzymes. Notably, inflammation and inflammatory mediators are some of the leading causes of cancer. Abnormal secretion of cytokines like interleukins (ILs), stromal-derived factor1/CXCL12-CXC, and tumor necrosis factor -α increase the chances of malignancy and subsequent abnormal cell production. These inflammatory mediators alter other cellular functions, increasing the likelihood of lung cancer development. For instance, activated IL-1β enhances P65 phosphorylation by linking and activating IKβ kinase (IKK) α/β. This causes an up-regulation of NF-kB levels. Moreover, IL-1β also up-regulates PKCαdependent c-JNK1/2, plasminogen activator expression, PI3K/AKT, and growth factor receptors and plays a critical role in lung cancer progression. It stimulates IJ- 15-hydroxyprostaglandin dehydrogenase and up-regulates Mitogen-activated protein kinase, phosphoinositide-3-kinase–protein kinase B/Akt (PI3K/AKT), JAK Signal transducer, and activator of transcription 6, and Protein kinase C pathways. Furthermore, oxidative stress is another major risk factor for lung cancer. It promotes pulmonary inflammation and enhances mechanisms of carcinogenesis (Kumari et al. 2023) **(Figure 1).**

Various factors such as consuming tobacco, smoking, environmental pollution, unhealthy lifestyle, and stress-induced reactive oxygen species (ROS) and reactive nitrogen species (RNS), which further cause oxidative damage to the DNA, macrophage stimulation, and translation factors. Furthermore, mitochondrial dysfunction is another major cause of lung cancer. An increase in the production of ROS, RNS, and various cytokines is responsible for mitochondrial oxidative damage. This damage induces a promotion of endoplasmic reticulum dysfunction, and reduced protein synthesis. Studies also reported that increased intracellular ROS causes abnormalities in the electron transport chain and disables the function of complex I-IV (Kumari et al. 2023) **(Figure 1).**

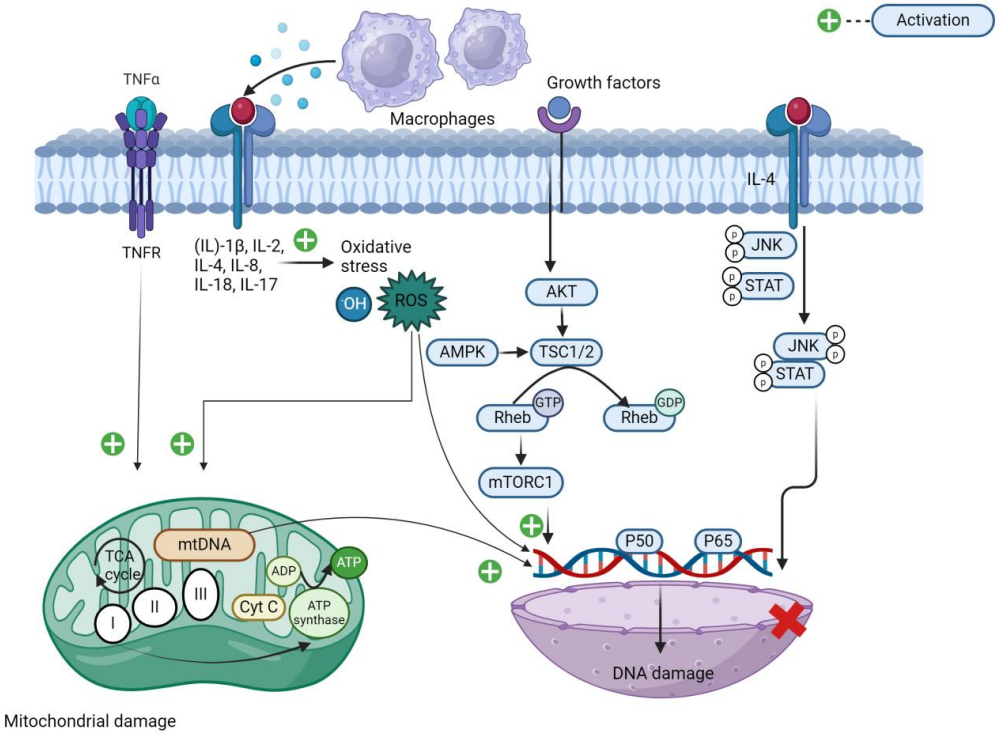

Figure 1: Pathophysiology of Lung Cancer

3. Lung Cancer Treatment Protocols and Associated Challenges

The treatment approach in lung cancer depends on the stage, histology, genetic alterations, and patient's condition, and usually includes surgery, chemotherapy, radiotherapy, immunotherapy, and molecularly targeted therapy either alone or in combined modality.

Curative surgical resection is only recommended for medically fit patients with early stages of lung cancer, e.g., NSCLC [Stage I, Stage II, and Stage IIIA]. Whereas adjuvant platinum-based chemotherapy is recommended for stages II-IIIA disease with an absolute decreased risk of death by 5.4% at 5 years; however, the relapse rates with the rate of toxicity are high (Alexander, Kim, and Cheng 2020).

Despite a marked improvement in molecular targeted therapies and immunotherapies outcomes for NSCLC over the past two decades, a vast majority of advanced NSCLCs become resistant to current treatments and eventually progress (Wang, Herbst, and Boshoff 2021).

Recent trials on lung cancer patients revealed significant and sustained responses in patients treated with programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) checkpoint blockade immunotherapies. However, mounting evidence suggests that a loss of effective anti-tumor immunity is associated with lung tumor evolution (Qu et al. 2021).

Radiotherapy, especially using carbon ions, is valued for its low toxicity and precise tumor cell targeting. While there's a debate on cost-effectiveness compared to proton therapy, efforts in research that aim to create smaller, cost-efficient instruments for more affordable particle therapy are needed (Durante, Debus, and Loeffler 2021).

Moreover, soaring cancer drug prices are resulting in variable access and outcomes, particularly with low- or middle-income countries being the biggest victims of inequity. This adversely impacts cancer patients, especially younger patients, new

immigrants, and those without private health coverage (Leighl et al. 2021).

4. Plant-Based Therapeutic Agents against Lung Cancer

Plants can prove to be an invaluable source of anti-cancer therapeutic agents. Plant-based products are proven to have a role in lung cancer therapy and prevention by sensitizing conventional factors, extending patient survival time, avoiding adverse effects of chemotherapy, promoting physiological improvement, and ameliorating quality of life in pulmonary malignancy cases (Khosravifarsani et al. 2023). Following are a few examples of candidates that may transform traditional lung cancer treatment regimens.

4.1.Saussurea involucrata (Kar. & Kir.) Sch.Bip.

A study (Lv et al. 2020) explored the effects of hispidulin, a phytocompound extracted from *Saussurea involucrata* (Asteraceae) on lung cancer cells. In clinical practice, two extraction methods of *S. involucrate*, including water decoction and alcohol extraction, are prescribed to treat rheumatoid arthritis and cardiovascular diseases (Yang et al. 2022). Hispidulin is extracted from the ariel parts, including the flowers of *S. involucrata* (Yu et al. 2013). In the study by (Lv et al. 2020), hispidulin demonstrated potent anti-cancer effects in human non-small-cell lung cancer (NSCLC) cell lines NCI-H460 and A549 *in vitro* and *in vivo.* At the concentrations of 5 and 10 μM, the phytocompound inhibited the growth of NCI-H460 and A549 cells, while apoptosis was promoted via increased generation of ROS in a dose-dependent manner. Furthermore, hispidulin triggered apoptosis in NSCLC cells through upregulated expression of cleaved caspase-3 and cleaved poly [ADP-ribose] polymerase. Notably, glutathione (a selective ROS inhibitor) reversed the cancer-inhibitory effects. In the mice xenograft model, at the dose of 20 and 40 mg/kg, the endoplasmic reticulum stress-mediated NCI-H460 cells apoptosis was induced by hispidulin. This effect was also reversed upon treatment with an ER-stress inhibitor (tauroursodeoxycholic acid) (Lv et al. 2020).

4.1.Dendrobium chrysotoxum Lindl.

Erianin, a small-molecule compound, mainly extracted from the stem of *Dendrobium chrysotoxum* (Orchidaceae) (Qiao, Du, and Xie 2022), is a promising anti-tumor agent. Erianin is usually extracted from *D. chrysotoxum* by ethyl acetate extraction method (Patent 2010). A study assessed the anti-cancer effects of erianin via *in vitro* and *in vivo* methods. At a concentration of 0.25, 0.5nM, erianin induced apoptosis and G2/M phase arrest of cells, while inhibiting the migration and invasion of lung cancer cells *in vitro*. Moreover, in the mouse xenograft model of Lewis lung cancer, oral administration of erianin at the dose of 50, 35, and 10 mg/ kg/ day for 12 days significantly inhibited nodule growth and lowered the fluorescence counts of Lewis cells. Furthermore, the phytocompound treatment reduced the percentage vascularity of tumor tissues; on the other hand, it increased the number of apoptotic tumor cells and the thymus indices. Erianin up-regulated the levels of interleukin 2 and tumor necrosis factor-α, decreased IL-10 levels and the spleen index, and strengthened the immune function (Zhang, Xie, et al. 2021).

4.2.*Morus alba* L.

In a study, albanol B, obtained from the root bark extract of *Morus alba* (Moraceae) was investigated for anti-cancer outcomes in lung cancer cells. *In vitro* evaluations showed that at the dose of 10 and 30 μM, albanol B inhibited the proliferation of four human lung cancer cell lines (A549, BZR, H1975, and H226) and induced apoptosis, based on the cleavage of caspase-7 and PARP (poly (ADP-ribose) polymerase). Moreover, albanol B down-regulated *Bcl-2*, and induced cell cycle arrest at G2/M by down-regulating cyclin-dependent kinase 1 (*CKD1*) expression and cyclin *B1*. However, the natural compound up-regulated the expression of cyclin-dependent kinase inhibitor 1 (*p21)*. In addition, it increased the production of mitochondrial ROS. Interestingly, treatment with a mitochondrial antioxidant blocked

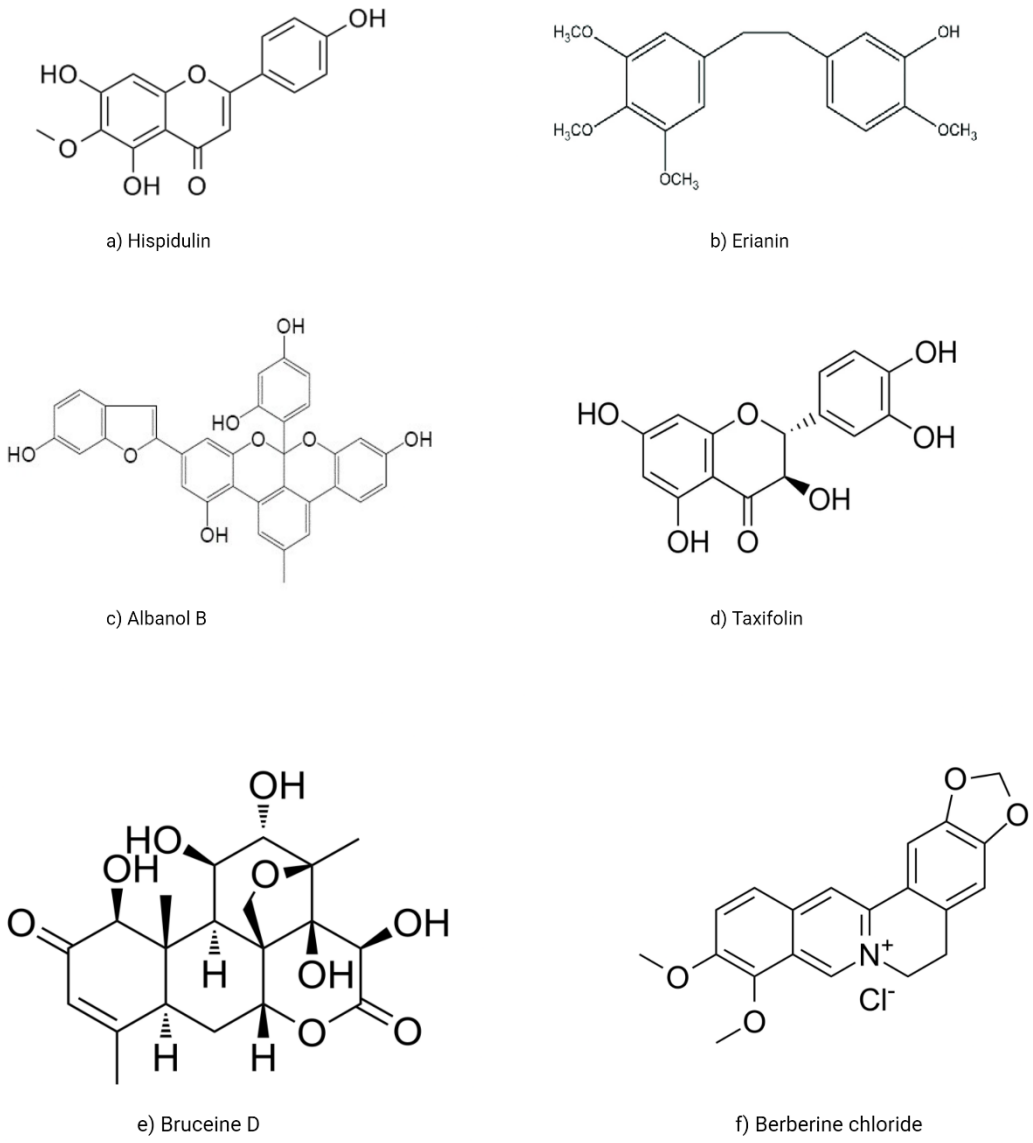

Figure 2: Chemical structure of selected phytocompounds effective against lung cancer

phytocompound-induced cell cycle arrest at G2/M and apoptosis, as well as the *p21* up-regulation. Whereas, the mitochondrial antioxidant down-regulated *CDK1* and *cyclin B1*. Moreover, at 50 and 100mg/kg/dose albanol-B significantly suppressed tumor growth in Lewis lung carcinoma tumor-bearing mice (Phan et al. 2020).

4.3. *Boletus edulis*

In a study, investigating the anti-cancer potentials of *Boletus edulis* (Boletaceae), Boletus edulis protein (BEAP) was isolated from *B. edulis* dried fruit bodies and purified via ion-exchange chromatography. The results demonstrated a potent anti- non-small-cell lung cancer effects were produced by BEAP in both *in vivo* and *in vitro* settings. *In vitro*, the cytotoxicity of BEAP was mediated by apoptosis induction and arrest of A549 cells in the G1 phase of the cell cycle. Furthermore, *in vivo*, BEAP significantly

suppressed the growth of A549 solid tumors (Zhang, Zhou, et al. 2021).

4.4. *Pseudotsuga menziesii* (Mirb.) Franco

Taxifolin is a flavonoid extracted from *P. menziesii* (Pinaceae) bark (Liu et al. 2023). An investigation into the anti-tumor effects of taxifolin utilized A549 and H1975 cells, whereas A549 xenograft BALB/c mice were used for *in vitro* and *in vivo* analyses. Cell viability, stemness, mobility, and protein expression were tested with Cell counting kit-8 (CCK-8). CCK-8 demonstrated obvious toxicity of taxifolin to both cell lines at a higher dose. Taxifolin exhibited inhibitory effects on stemness and sphere formation, reduced protein expression of *SOX2* and *OCT4*, and reduced CD133-positive cells. Additionally, taxifolin decreased invasive cells, and reduced N-cadherin and vimentin, while increasing E-cadherin expression, indicating that epithelial-mesenchymal transition was inhibited. All of the effects observed were exhibited in a dose-dependent manner. Notably, A549 cells were more sensitive to taxifolin than H1975 cells. Moreover, taxifolin inactivated PI3K and TCF4 protein phosphorylation, and suppressed tumor growth in A549 xenograft BALB/c mice, with decreased *SOX2* and *OCT4* expression and inhibited PI3K and TCF4 (Wang et al. 2020).

***4.5. Brucea javanica* (L.) Merr.**

Isolated from the seeds of *B. javanica*, bruceine D is a phytocompound with antineoplastic activity against various cancers, including the pancreas, breast, lung, blood, bone, and liver. One of the studies evaluating its anti-lung cancer effects found that when human lung cancer cells were exposed to bruceine D, it inhibited their proliferation. *In vitro* results showed that after 24h, the IC_{50} values for A549 and NCI-H292 cells were 36.76 and 31.22 μM, respectively; at the 48h mark, the IC_{50} values were 17.89 and 14.42 μM, respectively. Notably, the phytocompound did not exhibit any apparent toxicity in human umbilical vein cells EA.hy926. Bruceine D also demonstrated the ability to induce mitochondria-mediated apoptosis of cancer cells, and in A549 and NCI-H292 cells treated with a 20 μM dose of the phytocompound complete autophagic flux was observed. Additionally, bruceine D significantly improved intracellular ROS levels. Whereas, *In vivo*, tumor-bearing mice received injections of bruceine D 40 mg/kg for 15 days, the results showed growth inhibition in lung cancer xenografts (Fan et al. 2020).

4.6. *Berberis aristata* DC.

In a study, researchers delved into the impact of berberine chloride, a compound derived from *Berberis aristata* (Berberidaceae), on NSCLC. The results revealed that berberine chloride significantly inhibited the proliferation and colony formation of NSCLC cells in a dose- and time-dependent manner. Results showed that after a 72 h-treatment IC_{50} of berberine chloride against NCI-H460, A549, and NCI-H1299 cells were 30.3 μM, 44.5 μM, and 43.8 μM respectively, indicating that NCI-H460 cells are more sensitive to the phytocompound. Furthermore, berberine chloride-induced DNA double-stranded breaks by down-regulating the level of *TOP2B*, leading to NSCLC cell apoptosis. Additionally, berberine chloride was found to decrease Sin3A expression (a protein binding to TOP2B promoters) and shorten its half-life, further contributing to the down-regulation of TOP2B in NSCLC cells (Chen et al. 2020).

***4.8. Marsdenia tenacissima* (Roxb.) Moon**

M. tenacissima (Apocynaceae) is a traditional Chinese medicine with a history dating back to the Ming dynasty. A study aiming to uncover the mechanisms underlying its therapeutic efficacy and anti-cancer effects was conducted. Among 223 components of *M. tenacissima* studied through drug-like and pharmacokinetic analysis, the study identified petroleum ether and ethyl acetate extracts as particularly potent in inhibiting lung cancer cells. These extracts demonstrated significant inhibitory effects, with an IC_{50} value of 0.35 mg/ml indicating their effectiveness. Morphological changes characteristic of apoptosis were observed in treated lung cancer cells as compared to the control group (Hu et al. 2020).

Table 1. Summary of Plants, Phytocompounds, and Doses for Lung Cancer Treatment

Common Name	Family	Scientific Name	Part used	Chemical Constituent	Dose/ Binding Energy	Extract	Study Type/ Target	Citations
Snow Lotus	Asteraceae	*Saussurea involucrata*	Ariel parts	Hispidulin	*In vitro:* 15 and 30 μM *In vivo:* 20 and 40 mg/kg	Aqueous and alcohol	*In vitro* and *In vivo*	(Lv et al. 2020)
Fried-Egg Orchid	Orchidaceae	*Dendrobium chrysotoxum Lindl.*	Stem	Erianin	*In vitro:* 0.125, 0.25, 0.5nM *In vivo:* 10, 35, 50mg/kg Binding affinity: PI3K= −7.0, Akt= −8.2, mTOR= −7.1 kcal/mol	Ethyl acetate	I*n vitro* and *In vivo*	(Zhang, Xie, et al. 2021)
White Mulberry	Moraceae	*Morus alba*	Twigs/ root bark	Albanol B	*In vitro:* 10 and 30 μM *In vivo:* 50 and 100mg/kg	Methanol, n-hexane, dichloromethane, and ethyl acetate.	*In vitro* and *In vivo*	(Phan et al. 2020)
king mushroom, Porcini	Boletaceae	*Boletus edulis*	Dried fruit bodies	Boletus edulis protein (BEAP)	-	-	*In vitro* and *In vivo*	(Zhang, Zhou, et al. 2021)
Douglas Fir	Pinaceae	*Pseudotsuga menziesii*	Bark	Taxifolin	*In vitro:* 25, 50, and 100 μM/L	-	*In vitro*	(Wang et al. 2020)
Macassar Kernels	Simaroubaceae	*Brucea javanica*	Seed	Bruceine D	*In vitro:* IC50 (24h) A549 cells= 36.76 μM, NCI-H292 cells= 31.22 μM, IC50 (48h) A549 cells= 17.89 μM NCI-H292 cells= 14.42 μM *In vivo:* 40 mg/kg	-	*In vitro* and *In vivo*	(Fan et al. 2020)
Indian Barberry, Sumbal	Berberidaceae	*Berberis aristata*		Berberine chloride	*In vitro:* IC50 (72h) NCI-H460= 30.3 μM A549= 44.5 μM NCI-H1299= 43.8 μM *In vivo:*25 mg/kg	-	*In vitro* and *In vivo*	(Chen et al. 2020)
Rajmahal Hemp	Apocynaceae	*Marsdenia tenacissima*	Stem		*In vitro:* IC50 0.35 mg/ml	Petroleum ether and ethyl acetate	*In vitro*	(Hu et al. 2020)

5. Discussion

The class-based undertones of lung cancer causes cannot be ignored. It is presumed that individuals living with low income are more likely to smoke and, hence at a higher risk of developing lung cancer; moreover, they are less likely to seek preventative healthcare interventions (Sayani et al. 2021). Building on this argument, lung cancer treatment would be even more financially draining, which leads to equity concerns. Therefore, the search for novel cures, including those from herbal sources, is essential for expanding treatment options and cost optimization. Numerous studies have proven the efficacy of plants and phytocompounds (Figure 3). For instance, tannins from different plant sources such as cacao liquor, green tea leaf, cranberry, and grape have been shown to possess anti-cancer effects in the lungs (Rajasekar et al. 2021). Another example includes myricetin, a secondary metabolite flavonoid, found in a diverse range of consumable plant parts like *Hovenia acerba*, which has a potential against several classes of cancer, including lung cancer (Rajendran et al. 2021). Similarly, quinonoids, including phenanthrenequinones, naphthoquinones, and anthraquinones, constitute a large group of bioactive phytocompounds with anti-cancer effects, especially in lung cancer research. These compounds potentially promote apoptosis, induce autophagy, and inhibit proliferation, angiogenesis, and cell invasion and migration (Ying et al. 2020). Interestingly, through research on vegetal anti-cancer agents, dietary-based cancer prevention regimens and recommendations may be devised for cancer patients (Sukprasansap and Chanvorachote 2022). Most of the plants reviewed in this manuscript have been proven to be effective against lung cancer cells in both *in vivo* and *in vitro* settings. However, further studies are needed to evaluate their clinical potential in human subjects. An appropriate drug-delivery system is a crucial link that requires more attention in the quest for lung cancer therapy. In addition to the limited choices in terms of affordable and effective first-line chemotherapeutics, and resistant tumors, the non-optimal route of administration contributes to poor prognosis and high mortality in lung cancer. One suitable option could be drug Nano-carriers, administered via inhalation, which may prove to be an effective alternative strategy (Kumbhar et al. 2022). Whether phytocompounds can be administered through this route, the impact on efficacy and site-specific release through the inhalation route using an appropriate inhalation device needs further intellectual and financial resource allocation.

Additionally, a lack of scientific evidence to evaluate the safety and efficacy of herbal drugs adds to the challenges, as the quality of the trial drug has to be tested for batch-to-batch uniformity of the active constituents. Moreover, in clinical trials, a placebo for herbal drugs remains an arduous task due to difficulties with attaining identical color, smell, and taste of the herbal drug. However, these hurdles can be overcome by applying the most recent methodologies and guidelines for clinical trials (Parveen et al. 2015).

Furthermore, herbal remedies are cheaper and readily available; however, reckless utilization of phytocompound-based treatments threatens the sustainability of several plant species. Fortunately, in countries like India, traditional medicines are protected under the Drugs and Cosmetics Act of 1940 and the Drugs and Cosmetics Rules of 1945 (Parveen et al. 2015).

6. Conclusion

Plant-based anti-cancer treatment has the potential to revolutionize the cancer therapy landscape. They may be relatively safer, cheaper, and more efficacious choices than traditional therapies. Notably, many natural compounds, like hispidulin from *S. involucrate*, and bruceine D from *B. javanica* induced apoptosis in cancer cells. These phytocompounds demonstrated anti-cancer properties not only *in vitro* but also *in vivo.* The potent anti-cancer activity was exhibited by hispidulin by

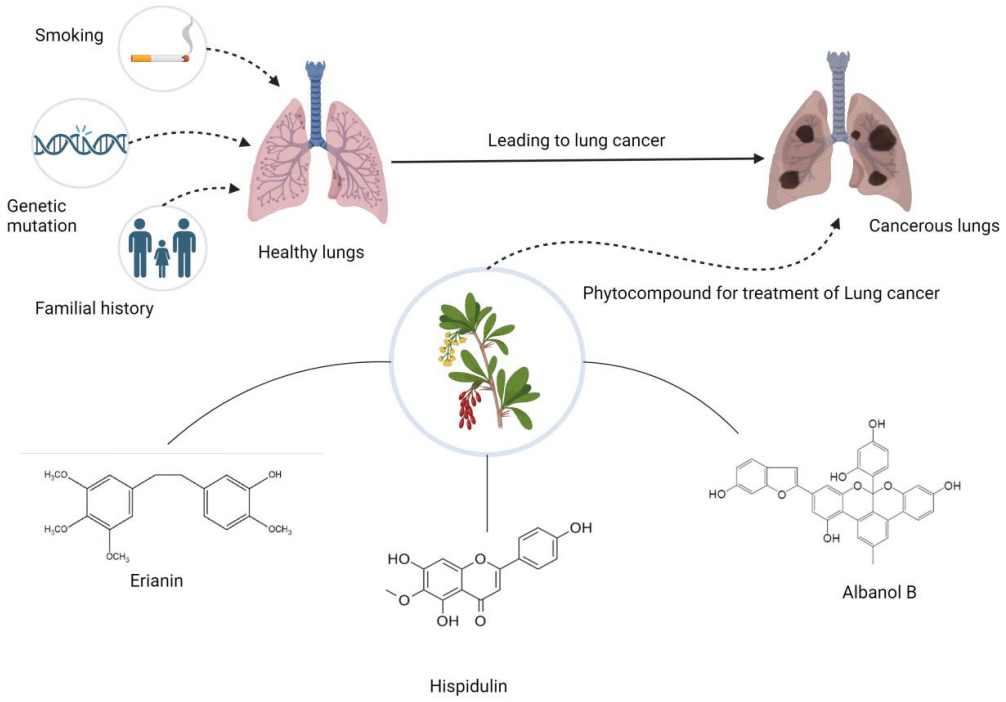

Figure 3: Summary of the phytocompounds action for treating lung cancer.

inducing apoptosis via increased generation of ROS in a dose-dependent manner, which was confirmed by using glutathione. Similarly, BEAP also led to the arrest of A549 cells in the G1 phase of the cell cycle via apoptosis induction. However, berberine chloride-induced DNA double-stranded breaks, by down-regulating the level of *TOP2B,* led to NSCLC cell apoptosis. Additionally, berberine chloride was found to decrease Sin3A expression, further contributing to the down-regulation of TOP2B in NSCLC cells. Another promising candidate for lung cancer treatment is *M. tenacissima,* as its components were active against cancer cells at a meager concentration of 0.35mg/ml. Additionally, erianin has also produced encouraging results *in vitro* and in *vivo*, as well as demonstrated a strong binding affinity with PI3K= −7.0, Akt= −8.2, and mTOR= −7.1 kcal/mol. With wide-scale replication of these studies, including clinical trials, with ample resource investment novel lung cancer therapeutic agents can be produced.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

There was no specific funding sought for this research study.

Study Approval

NA

Consent Forms

NA.

Data Availability

All the data related to this manuscript are available with the authors**.**

Author Contributions

Main idea and conceptualization, and initial draft by NS, literature collection, and review by NS, graphics, language, and grammar by AH and AS, analysis and proofreading by NS, AH, and AS, review editing, rebuttals, and final draft by, AMA, AAJJ, and NS.

Acknowledgments

NA

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