Indian Journal of Health Care, Medical & Pharmacy Practice (Vol 7, Issue 1, Jan-June 2026)
Home page of the journal: https://ijhmp.com/Home

Review Article

THERAPEUTIC POTENTIALS OF PHYTOCHEMICAL INTERVENTIONS IN CHEMICAL-INDUCED LUNG CANCER

Uday Kumar Panigrahi[1]* , Megha Jha[2]

[1]PhD Scholar, [2]Professor, Department of Life Science, Mansarovar Global University, Sehore, M.P., India.

Corresponding Author*: Uday Kumar Panigrahi, PhD Scholar, Department of Life Science, Mansarovar Global University, Sehore, M.P., India.

Email ID: udaypanigrahi1998@gmail.com

Orcid ID: https://orcid.org/ 0009-0000-3095-5498

DOI: https://doi.org/10.59551/IJHMP/25832069/2026.7.1.117

How to cite this article: Panigrahi UK, Jha M. Therapeutic Potentials of Phytochemical Interventions ni Chemical-Induced Lung Cancer. *Indian J. Health Care, Med. Pharm. Pract.* 2026;7(1):143-152.

Received: 17 March, 2026, Decision for Acceptance: 21 April, 2026

ABSTRACT

Phytochemicals, naturally occurring compounds found in plants, have garnered significant attention for their potential in preventing and managing various diseases, including lung cancer. Among the diverse classes of phytochemicals, polyphenols stand out due to their antioxidant and prooxidant properties. These compounds, such as the phenolic component piperine from Piper nigrum and Piper longum, have demonstrated cytotoxic and apoptotic effects on lung cancer cells. Common sources of phytochemicals include fruits, vegetables, herbs, and spices, which have traditionally been used for their medicinal properties. Phytochemicals exert their effects through multiple mechanisms, including antioxidant, anti-inflammatory, pro-apoptotic, and cell-cycle inhibition actions. For instance, antioxidants like catechin, cyanidin-3-glucoside, and kaempferol help scavenge reactive oxygen and nitrogen species, thereby preventing oxidative damage that can lead to cancer. Anti-inflammatory phytochemicals such as resveratrol and curcumin modulate inflammatory pathways, while compounds like quercetin and genistein induce apoptosis in cancer cells. Clinical trials have begun to explore the efficacy of these compounds in enhancing the response to conventional cancer treatments, reducing side effects, and overcoming therapeutic resistance. Despite their promising potential, challenges such as bioavailability, metabolism, and safety must be addressed to fully integrate phytochemicals into clinical practice. Advances in nanotechnology and formulation improvements offer potential solutions to these challenges, paving the way for safer and more effective cancer therapies.

KEYWORDS: Phytochemicals, Lung Cancer, Polyphenols, Antioxidants, Anti-inflammatory, Apoptosis, Clinical Trials, Bioavailability, Nanotechnology, Cancer Therapy.

Introduction

Overview of Lung Cancer: Incidence, Mortality, and Leading Causes

Lung cancer is a leading cause of global cancer incidence and associated mortality. According to GLOBOCAN 2022, lung cancer contributed 12.4%, which is around 2.5 million new cases to the global cancer burden and were responsible for 18.7% or 1.8 million cancer-related deaths[1]. In the U.S., lung cancer remains the leading cause of death in men over 40 years and women over 59 years of age. However, the average age of lung cancer diagnosis is around 70 years, with a majority of cases being reported between the age range of 55-74 years old[2]. Tobacco smoking remains one of the significant risk and causing factors of lung cancer as increased lung cancer incidence coincides with the rise in the tobacco industries. Since men smoke more in comparison to women, global lung cancer incidence and mortality are

twice as high as in men. Recently, due to the advent of tobacco smoking in women, a significant rise has been observed in the number of lung cancer cases in women[3]. Owing to the diverse number of risk factors involved, there is a significant difference in the nationwide prevalence and mortality of lung cancers. European countries, including Asian countries, specifically Western Asia, are leading in terms of lung cancer incidence rates, whereas Hungary, followed by Siberia, leads in terms of mortality rates[4]. Apart from smoking and secondhand smoking, air pollution, hereditary infections like tuberculosis, and occupational risk factors like exposure to asbestos, radon, arsenic, and other carcinogenic chemicals are leading causes of lung cancer incidence[2].

Definition and Significance of Chemical-induced Lung Cancer

It is now widely accepted that the gene-environment interaction plays a significant role in cancer initiation, development, and progression. Exposure to environmental carcinogens like a wide variety of chemicals has been recently studied with respect to the incidence of lung cancer. Lung cancers caused by exposure to chemical carcinogens are termed chemical-induced lung cancers. These chemical carcinogens majorly include tobacco smoke, asbestos, aflatoxin, chromium, arsenic, cadmium, mustard gas, radon, silica, uranium, vinyl chloride, petroleum-based products like gasoline, chloromethyl ethers, diesel exhaust, and coal products[5,6]. Chemical-induced lung cancers pose a significant burden to lung cancer-associated deaths. Around 80% of lung cancer-associated deaths were attributed to smoking. Air pollution was responsible for 108,000 deaths, utilization of solid fuel or coal resulted in 36,000 deaths, and even secondhand smoking was estimated to be responsible for 21,000 deaths[6].

Importance of Exploring Alternative and Complementary Therapies

Lung cancer pose severe health hazards that include a variety of symptoms, majorly presenting with a persistent cough that gets worse, occasionally spitting blood as cancer advances. Other reportedly common symptoms include chest pain, loss of appetite, shortness of breath, wheezing, and fatigue, which are consistent with weight loss. The symptoms manifest according to the age and health standards of the patient, where stage and anatomical location of the cancer further aggravate the condition[7]. Numerous treatment modalities have been adapted for the treatment of lung cancers that again depend upon the symptoms, overall health, tumor site and the stage of cancer. For early-stage lung cancers, surgery remains the primary treatment option, but if the tumor is not resectable, other options like radiotherapy and chemotherapy separately or in combination are often used. Some recent developments include targeted immunotherapy, laser therapy, photodynamic therapy and cryosurgery[8]. However, each treatment modality mentioned above is not only majorly unaffordable but also has potential side effects where some are manageable while others may pose a significant burden on the overall quality of life. Therefore, it is of dire importance that researchers should look for improved patient-friendly alternative therapeutics against this financially toxic global menace[9]. Exposure to chemical carcinogens such as polycyclic aromatic hydrocarbons (PAHs), arsenic, and asbestos plays a critical role in lung carcinogenesis by inducing oxidative stress, DNA damage, and activation of oncogenic pathways such as NF-κB and PI3K/Akt. These agents promote chronic inflammation, genomic instability, and uncontrolled cell proliferation. Phytochemicals, including curcumin, resveratrol, and quercetin, have been shown to counteract these effects by scavenging reactive oxygen species (ROS) and modulating key signaling pathways involved in tumor initiation and progression.

This article aims to review the therapeutic potentials of phytochemicals in the treatment and prevention of chemical-induced lung cancer.

Phytochemicals and their Sources

Definition and Classification

Phytochemicals are bioactive compounds secreted by plant sources (grains, fruits, herbs, nuts) as their protective mechanism against microbes, helminths, and viruses and exhibit strong antioxidant activities[10]. The phytochemicals from dietary and herbaceous sources have evidenced immense effects as anti-cancerous drugs and chemotherapeutic compounds or adjuvants[11].

Explanation of phytochemicals: naturally occurring compounds in plants

Phytochemicals are the secondary metabolites in plants that play significant roles in development and have protective functions against harmful agents and environmental stress[13]. They are characterized by possessing at least one aromatic ring and hydroxyl groups attached. They enhance plant reproduction using dispersal, pollination and germination and are also responsible for colours and flavours in plants[12]. They are also specific to plant species and exhibit an excellent source of medicinal utility. The nature and distribution of phytochemicals in individual plants also vary depending upon the plant tissue, although they are synthesized from carbohydrates via the phenylpropanoid or shikimate pathways[13].

Table 1: Molecular Mechanisms and Clinical Status of Key Phytochemicals in Lung Cancer Therapy

Phytochemical	Source	Molecular Mechanism of Action	Clinical Status
Quercetin	Apples, onions	Inhibits PI3K/Akt and NF-κB signaling, induces caspase-mediated apoptosis, and promotes cell cycle arrest	Preclinical/ early clinical trials
Resveratrol	Grapes, berries	Suppresses NF-κB and MAPK pathways, induces apoptosis via caspase-3 activation, and inhibits angiogenesis	Phase I/II clinical trials
Curcumin	Turmeric	Inhibits NF-κB, STAT3, and PI3K/Akt pathways, reduces proliferation, and induces apoptosis	Clinical trials ongoing
Genistein	Soybeans	Modulates estrogen receptor signaling and inhibits tyrosine kinases, leading to apoptosis and reduced tumor growth	Preclinical
EGCG	Green tea	Inhibits MAPK and PI3K/Akt pathways, reduces oxidative stress, and suppresses tumor cell proliferation	Clinical studies

Classification: flavonoids, alkaloids, terpenoids, polyphenols, etc

Based on the structural components found in the phytochemicals, they are majorly classified as alkaloids, polyphenols, glycosides, carotenoids, flavonoids, terpenoids, phytosterols, saponins and fibres[14-16]. Flavonoids are widely known phytochemicals with numerous medicinal benefits, such as reducing the risk of cardiovascular diseases, cancers, and aging[14]. Among all classes, the most found phytochemicals are polyphenols[17,18], which are rich in antioxidant and prooxidant properties. For example, the phenolic component 'piperine' found in Piper nigrum and Piper longum, commonly used in cooking as spices, has been reported to have cytotoxic and apoptotic effects on human lung cancer A549 cells[19].

Fruits, vegetables, herbs, and spices are common sources of phytochemicals and have been traditionally used for their medicinal properties. In the case of flavonoids, berries are regarded as a rich source in addition to cowpeas, dark chocolate, oregano, and green or black tea. Additionally, tea, coffee, and chocolate are rich in alkaloids. However, potatoes contain alkaloids that can be toxic, like solanine in potatoes. Marine phytoplankton, mushrooms, some plants and fungi are rich in terpenoids, whereas fresh foods contain high amounts of polyphenols.

Mechanisms of Action

There are numerous ways through which phytochemicals impart their medicinal properties. It majorly includes antioxidant, anti-inflammatory, pro-apoptotic, cell-cycle inhibitors, and anti-microbial actions. Here, they are introduced briefly.

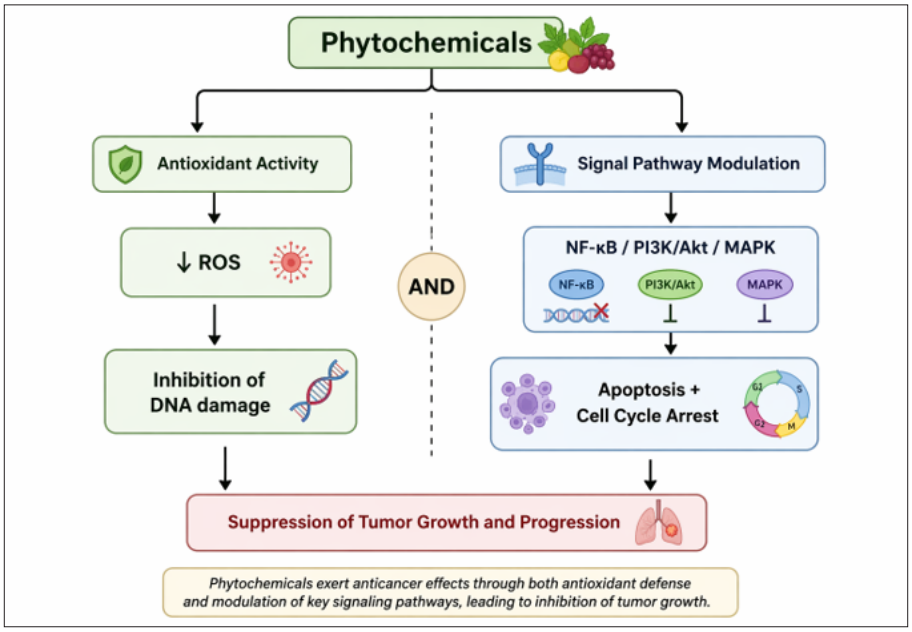

Figure 1. Mechanisms of Action of Phytochemicals in Lung Cancer Prevention and Therapy

ISSN 2583-2069

Antioxidant Activity

Most diseases result from the accumulation of oxidants commonly termed reactive oxygen species (ROS) and reactive nitrogen species (RNS). They accumulate in the cells because of normal metabolism, leading to pathogenesis. Therefore, it is essential to keep their concentration in check by scavenging them. Phytochemicals have been known to play an important role as antioxidants that are rich in fruits, grains, algae, fungi, and vegetables. The user input discusses the presence of antioxidant phytochemicals in fruits, vegetables, and cereal grains[20]. Even antioxidants are found in fruit wastes like peel and seed and in vegetables such as Chinese toon bud, ginseng leaf, and broccoli. They contain well-known antioxidant compounds like catechin, cyanidin 3-glucoside, epicatechin, gallic acid, kaempferol, and chlorogenic acid. Additionally, pigmented rice varieties like black, red, and purple rice contain high levels of antioxidant phytochemicals such as flavones and tannins[21]. The overproduction of the oxidant species in the cells can cause DNA damage or mutations that might later become carcinogenic[22]. In a study, older women's consumption of red wine, strawberries, vitamin C, or spinach was significantly associated with an increase in the total antioxidant capacity of serum[23].

Anti-inflammatory Effects

Another well-established medicinal property of the phytochemicals includes their anti-inflammatory role. Inflammation is one of the earliest symptoms that a disease often presents with. Inflammation is the immune system reacting to malfunctioning at the cellular or tissue levels. It is from the extensive and untreated inflammation that a tissue starts to damage. Inflammation is often caused, prolonged and mediated by the accumulation of oxidants like ROS and RNS[24]. As a result, the body launches anti-inflammatory mechanisms to alleviate the effects. However, that occasionally falls short of preventing the spread of inflammation. In such cases, numerous phytochemicals have been identified to play a significant role in modulating the inflammatory pathways to attenuate the heightened inflammatory response[25]. Phenolic phytochemicals like resveratrol, apigenin, astilbin, curcumin, and genistein are reported to suppress the action of pro-inflammatory molecules like Interferons (IFN-gamma), interleukins (IL-17,16,18), C-reactive proteins and TNF-alpha[26]. These molecules are essential components of the molecular signalling pathways that control inflammation at the cellular and tissue levels.

Induction of Apoptosis

Apart from the antioxidant and anti-inflammatory actions, the phytochemicals are known to function as pro-apoptotic. The induction of apoptosis is an essential medicinal property that can be used as a therapeutic against the proliferation of tumor cells. The role of phytochemicals in the regulation and mediation of programmed cell death has been explored by numerous studies across the globe. Phytochemicals like flavonoids, saponins, terpenoids, alkaloids, polyphenols, and coumarins have been found to regulate the pathways of programmed cell death that include the signalling of apoptosis, autophagy and pyroptosis[27]. Polyphenols like quercetin, catechins, apigenin, curcumin, rosmarinic acid, terpenoids like zeaxanthin, lutein and alkaloids like berberine are known to downregulate the anti-apoptotic molecules like BAX, p38, caspases and cytochrome-c. The downregulation of these molecules promotes apoptosis, which can be utilized as a therapeutic tool in the treatment of almost all cancers[28].

Inhibition of Proliferation

In addition to the pro-apoptotic roles, numerous phytochemicals have been identified that are known to interfere with the cell division process. By hampering cell division, these phytochemicals have found their application in the treatment of cancers, where the main aim of the drugs is to prevent the over-proliferation of the cells and prevent them from becoming tumors. Phytochemicals achieve this feat by inducing cell arrests at the different checkpoints of the cell cycle[29]. Such phytochemicals target three essential pathways that are actively involved in cellular proliferation, *viz* JAK-STAT, MAPK, and p53 pathways. Phytochemicals like curcumin, apigenin, and EGCG, which are majorly found in black and green tea, target these pathways to cause ani-proliferative effects in cancers[30].

Epigenetic Modulation

Recent studies have explored and found the significance of phytochemicals in the modulation of epigenetics. Since epigenetic modifications are strongly correlated with the expression of the genes, various phytochemicals have been identified that target different epigenetic mechanisms, leading to modifications in gene expression[31]. For example, phytochemicals like genistein, phenethyl isothiocyanate, curcumin, sulforaphane, organosulfur compound, resveratrol, and Indole-3-carbinol inhibit the deacetylation of histone proteins. In contrast, others like EGCG, genistein, and curcumin inhibit the acetylation of histone proteins. Additionally, phytochemicals such as EGCG, Genistein, organosulfur Compound, Lycopene, Phenethyl isothiocyanate, Curcumin, Sulforaphane, and Resveratrol inhibit the DNA methylation process by activating DNA methyltransferase enzymes[31].

Key Phytochemicals in Lung Cancer Treatment

Curcumin

The phytochemical curcumin is derived from the rhizome of *Curcuma longa* (turmeric). It has significant therapeutic potential in lung cancer treatment via different mechanisms, from inhibiting cell proliferation, migration, and invasion,

inducing apoptosis, to enhancing the chemotherapy effects through the modulation of different molecular pathways. Modulated doses of curcumin have been shown to inhibit lung cancer cell migration, invasion, and metastasis through the Rac1/PAK1 signalling pathway and downregulation of MMP-2 and MMP-9 expression[32]. Additionally, curcumin is known to suppress drug resistance in lung cancer cells, mainly by altering miRNA expression, such as downregulating miR-186*[33]. When it comes to the induction of the apoptotic pathways, curcumin was found to induce apoptosis in non-small cell lung cancer (NSCLC) cells through mechanisms involving calcium signalling pathways and Bcl-2 mediated IP3R phosphorylation[34].

Resveratrol

Resveratrol, a natural polyphenol found in red wine and various plants, has garnered significant attention for its potential therapeutic effects. Resveratrol is a natural component in red wine, grapes, and other plants. Resveratrol has been shown to inhibit lung cancer cell growth and metastasis, making it a promising chemo-preventive and chemotherapeutic agent. It operates through multiple mechanisms, including the induction of apoptosis, inhibition of metastasis, suppression of tumor-associated macrophages, induction of premature senescence, modulation of microRNA expression, and enhancement of radiosensitivity. These multifaceted actions underscore resveratrol's promise as a chemo-preventive and chemotherapeutic agent for lung cancer, supported by various studies demonstrating its efficacy and potential for improved delivery systems[35]. Resveratrol induces apoptosis by activating caspases and disrupting the mitochondrial membrane complex. It also causes cell cycle arrest in the G1 phase by up-regulating p53 and p21 [35]. Resveratrol was found to suppress the metastasis by inhibiting heme oxygenase-1 (HO-1) and matrix metalloproteinases (MMP-2 and MMP-9) through the NF-kappaB pathway [36].

Quercetin

Quercetin is a bioactive plant flavonoid commonly found in foods such as apples, onions, berries, and tea[37]. Quercetin has shown potential in preventing the progression of lung cancer and has synergistic effects with conventional chemotherapy drugs. Quercetin induces apoptosis in non-small cell lung cancer (NSCLC) cells by up-regulating apoptosis-related genes such as p53, Bax, and Fas and increasing the Bax/Bcl-2 ratio[38]. It enhances tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced cytotoxicity by increasing death receptor 5 (DR5) expression and suppressing survivin expression[39]. Additionally, quercetin modulates signalling pathways involved in cell proliferation, such as the Akt/MAPK/β-catenin pathway, and inhibits epithelial to mesenchymal transition (EMT)[40]. It also affects microRNA (miR) expression, particularly the tumor suppressor let-7 family and other carcinogenesis-related miRs[41]. Perhaps one of the surprising roles of quercetin is that it enhances the chemosensitivity of lung cancer cells to gemcitabine by inhibiting heat shock protein 70 (HSP70) expression, promoting apoptosis[42]. These findings suggest that Quercetin could be a valuable adjunct in lung cancer therapy, warranting further research to elucidate its therapeutic potential fully.

Genistein

Genistein is primarily found in soybeans and soy-based foods[43]. Genistein has shown potential as a chemotherapeutic agent against lung cancer by promoting apoptosis and inhibiting cell proliferation. Genistein promotes apoptosis in lung cancer cells through various pathways, including the IMPDH2/AKT1 and mitochondrial apoptosis pathways[44]. Another way through which Genistein is found to induce apoptosis is by activating caspase 3/9 and increasing reactive oxygen species formation[45]. Genistein can cause cell cycle arrest at the G2/M phase, which contributes to its antiproliferative effects [46]. Recent research has shown that Genistein can enhance the efficacy of other anticancer drugs like trichostatin A, adriamycin, docetaxel, and tamoxifen, suggesting its potential in combination therapies[43,47].

Table 2: Comparative Analysis of Curcumin, Resveratrol, and Quercetin in Lung Cancer Therapy

Parameter	Curcumin	Resveratrol	Quercetin
Source	Turmeric (*Curcuma longa*)	Grapes, berries	Apples, onions
Key Molecular Targets	NF-κB, STAT3, PI3K/Akt	NF-κB, MAPK, SIRT1	PI3K/Akt, NF-κB
Mechanism of Action	Anti-inflammatory, induces apoptosis, inhibits proliferation	Antioxidant, anti-inflammatory, promotes apoptosis	Antioxidant, induces apoptosis, inhibits tumor growth
Bioavailability	Very low	Very low (<1%)	Low
Pharmacokinetics	Poor absorption, rapid metabolism	Rapid hepatic metabolism	Rapid metabolism
Clinical Status	Clinical trials ongoing	Phase I/II trials	Early clinical studies
Major Limitation	Poor solubility	Low stability and rapid clearance	Poor absorption

ISSN 2583-2069

Therefore, in summary, phytochemicals are compounds naturally found in plants with promising potential in preventing and managing lung cancer. Numerous *in vitro* and *in vivo* studies have investigated their modes of action, effectiveness, and possible use as supplementary treatments alongside standard therapies. In addition to the induction of programmed cell death, phytochemicals have been known to sensitize lung cancer cells to chemotherapeutic drugs, enhancing their efficacy and potentially reducing the required dosage and associated side effects[48]. In vivo studies, such as the one done in mice NSCLC xenografts to study the antiproliferative effects of soy phytochemicals, were reported to decrease tumor proliferation, increase apoptosis, and induce necrosis within the tumors. The modulation of the Akt-signaling pathway was identified as a critical mechanism in this process[49]. Compounds such as curcumin, resveratrol, and quercetin have shown promise in targeting cancer stem cells associated with chemoresistance and, therefore, improving treatment outcomes[50]. Animal models are crucial as preclinical screening models in validating these effects and guiding the development of phytochemical-based lead compounds worth therapeutic application. With extensive data available from in-vitro and in-vivo studies on the efficacy, toxicity, pharmacokinetics, and safety of a phyto-derived lead compound, it becomes clear that human clinical trials should proceed. Integrating these natural compounds into lung cancer treatment regimens could offer safer and more effective therapeutic options.

Clinical Trials

Around half of the anticancer drugs approved between 1940 and 2014 have their origins in natural products or are directly derived from them[51]. Clinical trials involving phytochemicals for cancer treatment are still in the early stages despite developing many potential anticancer compounds. These trials focus on three main areas: enhancing the response of cancer cells to standard chemotherapy and radiotherapy, minimizing the severe side effects of standard cancer treatment, and identifying any unwanted interactions with standard therapy. Preclinical research has demonstrated the effectiveness of various phytochemicals, such as berberine, curcumin, green tea, catechins (including EGCG), lycopene, quercetin, resveratrol, and sulforaphane. Following are the phytochemicals that are currently in clinical trials for various cancers[52].

- Berberine (NCT03281096) for colorectal cancer, assessing prevention of recurrence.
- Curcumin (NCT03072992) for advanced and metastatic breast cancer, assessing quality of life, safety in combination, progression-free survival, time to disease progression, and time to treatment failure.
- Epigallocatechin (NCT02891538) for colorectal cancer, assessing change in methylation pattern compared to baseline.
- Lycopene (NCT03167268) for metastatic colorectal cancer assesses effectiveness in reducing skin toxicity alone or combined with panitumumab and pharmacokinetics.
- Quercetin (NCT01912820) for prostate cancer, assessing EGCG, ECG, Quercetin, and their methylated metabolites in prostate tissue and plasma, enzyme activity expression of COMT, DNMT1, and MRP1, and inter-individual variation in the genotype of COMT.
- Resveratrol (NCT01476592) is used for low-grade GI neuroendocrine tumors to assess Notch1 activation and toxicity.
- Sulforaphane (NCT03232138) for former smokers at high risk of developing lung cancer, assessing bronchial dysplasia index, cell proliferation marker Ki-67, and apoptosis markers including caspase-3 and TUNEL.

Critical Points

Curcumin, Resveratrol, and Quercetin have been extensively studied for their anticancer potential, with reported clinical dose ranges of approximately **500 mg to 8 g/day for curcumin**, **250 mg to 5 g/day for resveratrol**, and **500–1000 mg/day for quercetin**. Despite their promising biological activities, these phytochemicals exhibit significant pharmacokinetic limitations. They generally show **poor absorption and low oral bioavailability**, primarily due to limited aqueous solubility and instability in physiological conditions. Additionally, they undergo **extensive first-pass metabolism**, including glucuronidation and sulfation in the liver and intestines, resulting in rapid conversion to less active metabolites. Their **rapid systemic elimination and short half-lives** further reduce their therapeutic efficacy. These challenges highlight the need for advanced delivery systems, such as nanoparticles and liposomal formulations, to enhance their bioavailability and clinical effectiveness in lung cancer therapy. Despite the potential benefits of phytochemicals in therapeutics, their efficacy, potency, bioavailability, and metabolism present various challenges and opportunities for research and clinical applications.

Efficacy and Potency

Among the variables associated with the efficacy and potency of phytochemical-based therapeutics, genetic differences, such as single nucleotide polymorphisms (SNPs), can significantly influence the bioavailability and dosage of phytochemicals, affecting their therapeutic efficacy[53,54]. Furthermore, the potency of phytochemicals can vary systematically with cell line and drug class, indicating that factors other than potency, such as the slope of the dose-response curve and maximum effect (Emax), should be considered meticulously before drawing out the conclusion[55].

Comparison of effectiveness between phytochemicals and conventional therapies

Since cancers are heterogeneous, studies have found that

monotherapy with anticancer drugs is not effective in treating different types of cancer. Additionally, existing anticancer drugs face several challenges, including drug resistance, cancer cell insensitivity, adverse effects, and patient inconvenience. Therefore, phytochemicals derived from plants could serve as a more favourable alternative to traditional chemotherapy for cancer treatment due to their various properties, such as reduced adverse effects, action through multiple pathways, and cost-effectiveness. However, various preclinical studies have demonstrated that combining phytochemicals with conventional anticancer drugs is more productive than individually treating cancer because plant-derived compounds have lower anticancer efficacy than conventional anticancer drugs. Moreover, phytochemicals suffer from poor aqueous solubility and reduced bioavailability, which must be resolved for the efficacious treatment of cancer[56]. Therefore, a similar approach was utilized by Robert et al., who targeted the breast cancer cells with curcumin alone and combined with docetaxel and concluded the benefits of the phytochemical in lowering the adverse effects of chemotherapeutics being used[57]. Despite the studies claiming the synergistic benefits of such combinational therapy to this date, none in practice, majorly because of research gaps and insufficient data generated from the preclinical studies to push them into clinical trials. The factors that affect phytochemical bioavailability, including food processing, digestion, and cellular transport mechanisms[58], are mainly unknown and have become the primary reason for their insufficiency to be translated into clinical settings.

Strategies to enhance bioavailability (e.g., formulation improvements)

Modern-day research with the advent of nanotechnology has given birth to nanomedicine, which has possible answers to the bioavailability issues of phytochemical-based therapeutics. There is strong evidence in the form of in vitro studies that have found the codelivery of phytochemical and conventional chemotherapeutics synergistically not only prevents limiting the dosage but also has alleviated the toxicity and lowered the chances of chemoresistance of chemotherapeutics[56]. Currently, various nanocarriers are being considered for this purpose, including solid lipid nanoparticles, Nano-emulsions, micelles, liposomes, and nanotubes[59].

Assessment of the safety profile of phytochemicals

Phytochemicals are generally considered safe because they are naturally occurring, but there have been reported cases of toxicity and potential health risks. While there is a significant amount of data from laboratory studies, there is still limited information on their effectiveness, dosage levels and safety in living organisms. Phytochemicals have been reported to cause adverse effects such as skin irritation, sensitization, phototoxicity, and allergies[60]. For instance, phytochemicals derived from *Uvaria chamae* showed protective roles for DNA but also were found to cause haematological changes, indicating potential immune system enhancement[61]. Similarly, extract from *Zephyranthes citrina* was found to cause some minor alterations in blood parameters although no major toxicity was reported[62]. While supporting these claims, recent data from the United States between 2013-2014 reported a rise in herbal and dietary supplements that has resulted in 20% of all liver injuries[63]. This data strongly warrants the safety assessment of all phytochemical-based products before their use and commercialization. The safety assessment majorly involves the analysis of phytochemical properties, contamination levels, and the estimation of toxicological endpoints using methods such as the Threshold of Toxicological Concern (TTC) and Dermal Sensitization Threshold (DST)[60].

Conclusion

In conclusion, phytochemicals are naturally occurring compounds found in plants that have shown significant potential in preventing and treating lung cancer. Various studies have highlighted their ability to target cancer stem cells, reduce therapeutic resistance, and enhance the efficacy of conventional treatments. The key phytochemicals such as curcumin, resveratrol, Quercetin, and epigallocatechin-3-gallate have been extensively studied for their chemo-preventive and anticancer mechanisms. These compounds majorly function by modulating multiple cellular signalling pathways, including those involved in apoptosis, autophagy, and oxidative stress, thereby inhibiting cancer cell proliferation and metastasis. Phytochemicals have the potential to prevent cancer initiation and progression by exerting anti-inflammatory and antioxidant effects.

Additionally, phytochemicals were found to enhance the efficacy of chemotherapeutic drugs and reduce their side effects. Various phytochemicals are known to specifically target cancer stem cells, which are often responsible for therapeutic resistance and tumor recurrence. Furthermore, phytochemicals combined with conventional therapies can enhance treatment efficacy and reduce drug resistance. However, such an approach faces bioavailability issues that advanced delivery systems like nanoparticles and liposomes can address. While preclinical studies have shown promising results, there is a pressing need for large-scale clinical trials to validate the efficacy and safety of phytochemicals in lung cancer treatment. The major focus of these clinical trials should be determining the optimal doses for maximum therapeutic benefit with minimal side effects and assessing the long-term impact of phytochemical interventions on patient survival and quality of life. From the analysis of the available literature, integrating phytochemicals into standard lung cancer treatment protocols could offer several benefits, from reduced side effects and enhanced efficacy to personalized treatment where phytochemicals can be tailored to target specific molecular profiles of lung cancer.

ISSN 2583-2069

Conflict of Interest

None

References

1. Li C, Lei S, Ding L, Xu Y, Wu X, Wang H, et al. Global burden and trends of lung cancer incidence and mortality. Chin Med J 2023;136:1583–90. https://doi.org/10.1097/CM9.0000000000002529.
2. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. Contemp Oncol (Pozn) 2021;25:45–52. https://doi.org/10.5114/wo.2021.103829.
3. Pesch B, Kendzia B, Gustavsson P, Jöckel K-H, Johnen G, Pohlabeln H, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. Int J Cancer 2012;131:1210–9. https://doi.org/10.1002/ijc.27339.
4. Lung cancer statistics | World Cancer Research Fund International n.d. https://www.wcrf.org/cancer-trends/lung-cancer-statistics/ (accessed May 20, 2024).
5. Fucic A, Gamulin M, Ferencic Z, Rokotov DS, Katic J, Bartonova A, et al. Lung cancer and environmental chemical exposure: a review of our current state of knowledge with reference to the role of hormones and hormone receptors as an increased risk factor for developing lung cancer in man. Toxicol Pathol 2010;38:849–55. https://doi.org/10.1177/0192623310378136.
6. Shankar A, Dubey A, Saini D, Singh M, Prasad CP, Roy S, et al. Environmental and occupational determinants of lung cancer. Transl Lung Cancer Res 2019;8:S31–49. https://doi.org/10.21037/tlcr.2019.03.05.
7. Lung Cancer Symptoms & Early Signs | City of Hope n.d. https://www.cancercenter.com/cancer-types/lung-cancer/symptoms (accessed May 20, 2024).
8. Lemjabbar-Alaoui H, Hassan OU, Yang Y-W, Buchanan P. Lung cancer: Biology and treatment options. Biochim Biophys Acta 2015;1856:189–210. https://doi.org/10.1016/j.bbcan.2015.08.002.
9. Boulanger M, Mitchell C, Zhong J, Hsu M. Financial toxicity in lung cancer. Front Oncol 2022;12:1004102. https://doi.org/10.3389/fonc.2022.1004102.
10. Kumar A, P N, Kumar M, Jose A, Tomer V, Oz E, et al. Major phytochemicals: recent advances in health benefits and extraction method. Molecules 2023;28. https://doi.org/10.3390/molecules28020887.
11. Shu L, Cheung K-L, Khor TO, Chen C, Kong A-N. Phytochemicals: cancer chemoprevention and suppression of tumor onset and metastasis. Cancer Metastasis Rev 2010;29:483–502. https://doi.org/10.1007/s10555-010-9239-y.
12. Martinez KB, Mackert JD, McIntosh MK. Polyphenols and intestinal health. Nutrition and functional foods for healthy aging, Elsevier; 2017, p. 191–210. https://doi.org/10.1016/B978-0-12-805376-8.00018-6.
13. Rabizadeh F, Mirian MS, Doosti R, Kiani-Anbouhi R, Eftekhari E. Phytochemical classification of medicinal plants used in the treatment of kidney disease based on traditional persian medicine. Evid Based Complement Alternat Med 2022;2022:8022599. https://doi.org/10.1155/2022/8022599.
14. Cassidy A, Kay C. Phytochemicals: classification and occurrence. Encyclopedia of human nutrition, Elsevier; 2013, p. 39–46. https://doi.org/10.1016/B978-0-12-375083-9.00226-9.
15. 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. https://doi.org/10.1016/j.fct.2020.111592.
16. Thakur M, Singh K, Khedkar R. Phytochemicals. Functional and preservative properties of phytochemicals, Elsevier; 2020, p. 341–61. https://doi.org/10.1016/B978-0-12-818593-3.00011-7.
17. Bayir AG, Kiziltan HS, Kocyigit A. Plant family, carvacrol, and putative protection in gastric cancer. Dietary interventions in gastrointestinal diseases, Elsevier; 2019, p. 3–18. https://doi.org/10.1016/B978-0-12-814468-8.00001-6.
18. Upadhyay S, Dixit M. Role of polyphenols and other phytochemicals on molecular signaling. Oxid Med Cell Longev 2015;2015:504253. https://doi.org/10.1155/2015/504253.
19. Turrini E, Sestili P, Fimognari C. Overview of the Anticancer Potential of the “King of Spices” Piper nigrum and Its Main Constituent Piperine. Toxins (Basel) 2020;12. https://doi.org/10.3390/toxins12120747.
20. Guo Y-J, Deng G-F, Xu X-R, Wu S, Li S, Xia E-Q, et al. Antioxidant capacities, phenolic compounds and polysaccharide contents of 49 edible macro-fungi. Food Funct 2012;3:1195–205. https://doi.org/10.1039/c2fo30110e.
21. Deng G-F, Xu X-R, Zhang Y, Li D, Gan R-Y, Li H-B. Phenolic compounds and bioactivities of pigmented rice. Crit Rev Food Sci Nutr 2013;53:296–306. https://doi.org/10.1080/10408398.2010.529624.
22. Zhang Y-J, Gan R-Y, Li S, Zhou Y, Li A-N, Xu D-P, et al. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. Molecules 2015;20:21138–56. https://doi.org/10.3390/molecules201219753.
23. Cao G, Russell RM, Lischner N, Prior RL. Serum antioxidant capacity is increased by consumption of strawberries, spinach, red wine or vitamin C in elderly women. J Nutr 1998;128:2383–90. https://doi.org/10.1093/jn/128.12.2383.
24. Bayry J, Radstake TR. Immune-mediated inflammatory diseases: progress in molecular pathogenesis and therapeutic strategies. Expert Rev Clin Immunol 2013;9:297–9. https://doi.org/10.1586/eci.13.10.
25. Shin SA, Joo BJ, Lee JS, Ryu G, Han M, Kim WY, et al.

Phytochemicals as Anti-Inflammatory Agents in Animal Models of Prevalent Inflammatory Diseases. Molecules 2020;25. https://doi.org/10.3390/molecules25245932.
26. Guo L, Liu W, Lu T, Guo W, Gao J, Luo Q, et al. Decrease of Functional Activated T and B Cells and Treatment of Glomerulonephitis in Lupus-Prone Mice Using a Natural Flavonoid Astilbin. PLoS ONE 2015;10:e0124002. https://doi.org/10.1371/journal.pone.0124002.
27. Zheng Z, Zhang L, Hou X. Potential roles and molecular mechanisms of phytochemicals against cancer. Food Funct 2022;13:9208–25. https://doi.org/10.1039/d2fo01663j.
28. Limanaqi F, Biagioni F, Mastroiacovo F, Polzella M, Lazzeri G, Fornai F. Merging the Multi-Target Effects of Phytochemicals in Neurodegeneration: From Oxidative Stress to Protein Aggregation and Inflammation. Antioxidants (Basel) 2020;9. https://doi.org/10.3390/antiox9101022.
29. Dhupal M, Chowdhury D. Phytochemical-Based Nanomedicine for Advanced Cancer Theranostics: Perspectives on Clinical Trials to Clinical Use. Int J Nanomedicine 2020;15:9125–57. https://doi.org/10.2147/IJN.S259628.
30. View of A REVIEW ON BIOACTIVE PHYTOCHEMICALS AND IT'S MECHANISM ON CANCER TREATMENT AND PREVENTION BY TARGETING MULTIPLE CELLULAR SIGNALING PATHWAYS | International Journal of Pharmacy and Pharmaceutical Sciences n.d. https://journals.innovareacademics.in/index.php/ijpps/article/view/42798/25742 (accessed May 22, 2024).
31. Shankar S, Kumar D, Srivastava RK. Epigenetic modifications by dietary phytochemicals: implications for personalized nutrition. Pharmacol Ther 2013;138:1–17. https://doi.org/10.1016/j.pharmthera.2012.11.002.\
32. Chen Q, Zheng Y, Jiao D, Chen F, Hu H, Wu Y, et al. Curcumin inhibits lung cancer cell migration and invasion through Rac1-dependent signaling pathway. J Nutr Biochem 2014;25:177–85. https://doi.org/10.1016/j.jnutbio.2013.10.004.
33. Zhang J, Zhang T, Ti X, Shi J, Wu C, Ren X, et al. Curcumin promotes apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells through an miRNA signaling pathway. Biochem Biophys Res Commun 2010;399:1–6. https://doi.org/10.1016/j.bbrc.2010.07.013.
34. Xu X, Chen D, Ye B, Zhong F, Chen G. Curcumin induces the apoptosis of nonsmall cell lung cancer cells through a calcium signaling pathway. Int J Mol Med 2015;35:1610–6. https://doi.org/10.3892/ijmm.2015.2167.
35. Whyte L, Huang Y-Y, Torres K, Mehta RG. Molecular mechanisms of resveratrol action in lung cancer cells using dual protein and microarray analyses. Cancer Res 2007;67:12007–17. https://doi.org/10.1158/0008-5472.CAN-07-2464.
36. Liu P-L, Tsai J-R, Charles AL, Hwang J-J, Chou S-H, Ping Y-H, et al. Resveratrol inhibits human lung adenocarcinoma cell metastasis by suppressing heme oxygenase 1-mediated nuclear factor-kappaB pathway and subsequently downregulating expression of matrix metalloproteinases. Mol Nutr Food Res 2010;54 Suppl 2:S196-204. https://doi.org/10.1002/mnfr.200900550.
37. Lam TK, Rotunno M, Lubin JH, Wacholder S, Consonni D, Pesatori AC, et al. Dietary quercetin, quercetin-gene interaction, metabolic gene expression in lung tissue and lung cancer risk. Carcinogenesis 2010;31:634–42. https://doi.org/10.1093/carcin/bgp334.
38. Li H, Tan L, Zhang J-W, Chen H, Liang B, Qiu T, et al. Quercetin is the Active Component of Yang-Yin-Qing-Fei-Tang to Induce Apoptosis in Nonsmall Cell Lung Cancer. Am J Chin Med 2019;47:879–93. https://doi.org/10.1142/S0192415X19500460.
39. Chen W, Wang X, Zhuang J, Zhang L, Lin Y. Induction of death receptor 5 and suppression of survivin contribute to sensitization of TRAIL-induced cytotoxicity by Quercetin in nonsmall cell lung cancer cells. Carcinogenesis 2007;28:2114–21. https://doi.org/10.1093/carcin/bgm133.
40. Elumalai P, Ezhilarasan D, Raghunandhakumar S. Quercetin Inhibits the Epithelial to Mesenchymal Transition through Suppressing Akt Mediated Nuclear Translocation of β-Catenin in Lung Cancer Cell Line. Nutr Cancer 2022;74:1894–906. https://doi.org/10.1080/01635581.2021.1957487.
41. Lam TK, Shao S, Zhao Y, Marincola F, Pesatori A, Bertazzi PA, et al. Influence of quercetin-rich food intake on microRNA expression in lung cancer tissues. Cancer Epidemiol Biomarkers Prev 2012;21:2176–84. https://doi.org/10.1158/1055-9965.EPI-12-0745.
42. Lee SH, Lee EJ, Min KH, Hur GY, Lee SH, Lee SY, et al. Quercetin enhances chemosensitivity to gemcitabine in lung cancer cells by inhibiting heat shock protein 70 expression. Clin Lung Cancer 2015;16:e235-43. https://doi.org/10.1016/j.cllc.2015.05.006.
43. Spagnuolo C, Russo GL, Orhan IE, Habtemariam S, Daglia M, Sureda A, et al. Genistein and cancer: current status, challenges, and future directions. Adv Nutr 2015;6:408–19. https://doi.org/10.3945/an.114.008052.
44. Xu H, Ma H, Zha L, Li Q, Pan H, Zhang L. Genistein promotes apoptosis of lung cancer cells through the IMPDH2/AKT1 pathway. Am J Transl Res 2022;14:7040–51.
45. Zhang J, Su H, Li Q, Li J, Zhao Q. Genistein decreases A549 cell viability via inhibition of the PI3K/AKT/HIF-1α/VEGF and NF-κB/COX-2 signaling pathways. Mol Med Report 2017;15:2296–302. https://doi.org/10.3892/mmr.2017.6260.
46. Lian F, Bhuiyan M, Li YW, Wall N, Kraut M, Sarkar FH. Genistein-induced G2-M arrest, p21WAF1 upregulation, and apoptosis in a non-small-cell lung

cancer cell line. Nutr Cancer 1998;31:184–91. https://doi.org/10.1080/01635589809514701.
47. Wu T-C, Lin Y-C, Chen H-L, Huang P-R, Liu S-Y, Yeh S-L. The enhancing effect of Genistein on apoptosis induced by trichostatin A in lung cancer cells with wild type p53 genes is associated with upregulation of histone acetyltransferase. Toxicol Appl Pharmacol 2016;292:94–102. https://doi.org/10.1016/j.taap.2015.12.028.
48. Wattanathamsan O, Hayakawa Y, Pongrakhananon V. Molecular mechanisms of natural compounds in cell death induction and sensitization to chemotherapeutic drugs in lung cancer. Phytother Res 2019;33:2531–47. https://doi.org/10.1002/ptr.6422.
49. Gallo D, Zannoni GF, De Stefano I, Mosca M, Ferlini C, Mantuano E, et al. Soy phytochemicals decrease nonsmall cell lung cancer growth in female athymic mice. J Nutr 2008;138:1360–4. https://doi.org/10.1093/jn/138.7.1360.
50. Heng WS, Kruyt FAE, Cheah S-C. Understanding Lung Carcinogenesis from a Morphostatic Perspective: Prevention and Therapeutic Potential of Phytochemicals for Targeting Cancer Stem Cells. Int J Mol Sci 2021;22. https://doi.org/10.3390/ijms22115697.
51. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs from 1981 to 2014. J Nat Prod 2016;79:629–61. https://doi.org/10.1021/acs.jnatprod.5b01055.
52. Choudhari AS, Mandave PC, Deshpande M, Ranjekar P, Prakash O. Phytochemicals in cancer treatment: from preclinical studies to clinical practice. Front Pharmacol 2019;10:1614. https://doi.org/10.3389/fphar.2019.01614.
53. Lampe JW, Chang J-L. Interindividual differences in phytochemical metabolism and disposition. Semin Cancer Biol 2007;17:347–53. https://doi.org/10.1016/j.semcancer.2007.05.003.
54. Borel P, Desmarchelier C. Bioavailability of Fat-Soluble Vitamins and Phytochemicals in Humans: Effects of Genetic Variation. Annu Rev Nutr 2018;38:69–96. https://doi.org/10.1146/annurev-nutr-082117-051628.
55. Fallahi-Sichani M, Honarnejad S, Heiser LM, Gray JW, Sorger PK. Metrics other than potency reveal systematic variation in responses to cancer drugs. Nat Chem Biol 2013;9:708–14. https://doi.org/10.1038/nchembio.1337.
56. Kumar G, Virmani T, Sharma A, Pathak K. Codelivery of Phytochemicals with Conventional Anticancer Drugs in Form of Nanocarriers. Pharmaceutics 2023;15. https://doi.org/10.3390/pharmaceutics15030889.
57. Bayet-Robert M, Morvan D. Metabolomics reveals metabolic targets and biphasic responses in breast cancer cells treated by curcumin alone and in association with docetaxel. PLoS ONE 2013;8:e57971. https://doi.org/10.1371/journal.pone.0057971.
58. Bohn T, McDougall GJ, Alegría A, Alminger M, Arrigoni E, Aura A-M, et al. Mind the gap-deficits in our knowledge of aspects impacting the bioavailability of phytochemicals and their metabolites--a position paper focusing on carotenoids and polyphenols. Mol Nutr Food Res 2015;59:1307–23. https://doi.org/10.1002/mnfr.201400745.
59. Hasani M, Abdouss M, Shojaei S. Nanocontainers for drug delivery systems: A review of Halloysite nanotubes and their properties. Int J Artif Organs 2021;44:426–33. https://doi.org/10.1177/0391398820968836.
60. Antignac E, Nohynek GJ, Re T, Clouzeau J, Toutain H. Safety of botanical ingredients in personal care products/cosmetics. Food Chem Toxicol 2011;49:324–41. https://doi.org/10.1016/j.fct.2010.11.022.
61. Akolade OR, Chinwe AS, Olalekan BT, Halima AT, Fatima AA, Emuejevoke TT, et al. Haematological and Genotoxicity Evaluations of Phytochemical Compounds from n-Hexane Extract of *Uvaria chamae* Stem on Selected Organs in Mice. Annals of Science and Technology 2018;3:28–34. https://doi.org/10.2478/ast-2018-0012.
62. Rehman MHU, Saleem U, Ahmad B, Rashid M. Phytochemical and toxicological evaluation of Zephyranthes citrina. Front Pharmacol 2022;13:1007310. https://doi.org/10.3389/fphar.2022.1007310.
63. Liu Y. Incorporation of absorption and metabolism into liver toxicity prediction for phytochemicals: A tiered in silico QSAR approach. Food Chem Toxicol 2018;118:409–15. https://doi.org/10.1016/j.fct.2018.05.039.