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REVIEW ARTICLE

Lung Cancer Management: A Comprehensive Review with Special Focus on Natural Remedies and Bioactive Compounds

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Abstract

Lung cancer is a significant global health concern, accounting for a substantial proportion of cancer-related morbidity and mortality worldwide. This review synthesizes current knowledge on the epidemiology, histopathological sub types, staging systems, and standard therapeutic approaches- including surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy- used in the management of lung cancer. Additionally, it highlights the emerging interest in natural remedies and bioactive natural products, such as alkaloids, phenolic compounds, sulfur-containing compounds, and terpenoids, which have demonstrated promising anticancer activities through various mechanisms, including apoptosis induction, cell cycle arrest, immune modulation, and signalling pathway inhibition. Traditional medical systems such as *Ayurveda* and traditional Chinese medicine are also discussed for their contributions to complementary and integrative therapeutic strategies. Despite these advancements, challenges such as therapeutic resistance, metastasis, and treatment-related toxicities persist. The review concludes by underscoring the importance of rigorous clinical validation, standardization, and translational research to fully harness the therapeutic potential of natural compounds and optimize integrative treatment paradigms in lung cancer care.

Major Findings: Bioactive natural compounds from diverse chemical classes demonstrate multi-target anticancer activities, while traditional medicine systems provide valuable complementary approaches. Integration of these into conventional therapy may improve lung cancer treatment outcomes.

Keywords: Lung Cancer, Natural Remedies, Non-small Cell Lung Cancer, Phytochemicals, Small Cell Lung Cancer, Traditional Medicine

1. Introduction

Lung cancer remains a grand enemy at the complex level of global health and is by far the leader of cancer-associated death at the worldwide level[1]. Within the context of the global health crisis, lung cancer emerged in 2020 as the leading cause of cancer-associated deaths, accounting for 18.2 % of all deaths at the hands of this deadly foe. Remarkably, it came out to be the second most common cancer in both genders, and it did so with a poignant difference: Although it was the most common form of cancer and the leading cause of death in males, in females it became the second largest killer among the cancer population and the third most common type[2].

According to estimates by the American Cancer Society, approximately 238,340 new lung cancer cases are expected to be diagnosed in 2023, with around 127,070 deaths anticipated[3]. Cigarette smoking remains the leading etiologic factor, accounting for about 80% of new lung cancer diagnoses[4].

Lung cancer is a major public health problem, and its epidemiology and impact have been areas of continued extensive research. Epidemiological studies have revealed risk factors and their impact in the development and prognosis of lung cancer. For instance, logistic challenges exist in the heavy reliance on detailed tobacco history and could be out of sync with shifts in the epidemiology of lung cancer[5].

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Epidemiological studies have continuously evolved to better understand lung cancer risk factors, which include tobacco smoke exposure and environmental pollutants such as PM2.5 particulate matter. Emerging data suggests an association of *Mycobacterium tuberculosis* infection with lung cancer incidence[6]. Cachexia, a syndrome of cancer-related weight loss and wasting, significantly affects chemotherapy outcomes and prognosis. Emerging epidemiological data does suggest that along with smoking, some dietary practices do have a possible link in influencing the rate of incidence of lung cancer[7]. Another research, based on an analysis of the population level, carried out with a population-level dataset to evaluate the effects of the combined impacts of various sources of low-dose radiation and PM2.5 on lung cancer incidences in the USA[8].

Accordingly, lung cancer is also the most common malignant tumour in China according to the recent report of cancer epidemiology. The mean age of death of Austrian male lung cancer patients unexpectedly decreased until 1996, and this epidemiological trend reversed after the mid-1990s until 2007, indicating that gender variations in lung cancer epidemiology have been also studied[9]. Further, the genetic epidemiology of lung cancer consortium analysed family histories for connections to lung cancer. The relationship of PM2.5 with lung cancer incidence, mortality, and survival status has been sketched out by epidemiological studies, but the mechanisms of carcinogenesis in PM2.5-associated lung cancer remain largely unclear[10].

On the other hand, epidemiologic studies have shown that higher serum 25-hydroxy vitamin D levels are related to a reduced risk of a number of cancer types, one of which is lung cancer[11]. Furthermore, lung cancer has become the largest burden on public health in China since it is the leading cause of cancer death in terms of morbidity and mortality. In addition, Global Cancer Epidemiology Statistics (GLOBOCAN2020) shows that lung cancer is still the deadliest cancer in the world[12]. Just like most of the other cancer, studies of epidemiology in lung cancer have also suggested that ß-AR signalling may have an impact on the incidence of lung cancer and its progression[13]. Therefore, in future studies of epidemiology and clinic importance, detailed smoking history must be included to predict the better management of lung cancer prognosis and treatment plans of the patients[14].

Early detection and improved treatment strategies greatly influence the outcomes of lung cancer patients. The relevance and impact of early detection on lung cancer cases contribute highly to time to treatment initiation and overall prognosis of a patient[15]. The recent innovations of technology in the field of radiotherapy have made tumoricidal doses apply to a very great precision while at the same time sparing damage to normal surrounding tissues, hence making radiotherapy a leading option in the treatment of lung cancer. Further, the recent development of targeted therapies and immune checkpoint inhibitors has transformed the management of lung cancer, with dramatic improvements in the outcomes of patient care over the last decade[16].

What is more, the approval of Pembrolizumab and Sintilimab as first-line treatments to treat advanced squamous cancer of lungs marked the reason for novel treatment options as part of promoting the fine patient care[17]. In a time of improved prognosis for patients with advanced non-small-cell lung cancer, interventions in the setting of cancer Cachexia gain even more importance. Recent advances have strikingly improved the understanding of molecular pathology in lung cancer, including driver mutations, which eventually led to the development of targeted strategies against the disease[18].

There exist disparities in survival and care- between patients with lung cancer, as well- across a range of social determinants of health, lending to the importance of the demonstration of equal opportunity through access to groundbreaking therapies and the need for more research in this inequality in approaches[19]. Immune checkpoint inhibitors have mainly taken the stage as a major therapeutic option in lung cancers, especially in advanced disease, for PD-L1-positive cases, with recommendations from major clinical guidelines. Additionally, its combination with the deep radiomics that were longitudinally profiled with aid of the data belonging to clinic has shown prospect predictive power with the durable benefits related to the immunotherapy, especially among advanced non-small cell lung cancer patients[20].

2. Types of Lungs Cancer

Lung cancer is categorized into 2 primary types based on histology:

- Non-Small Cell Lung Carcinoma (NSCLC) and
- Small Cell Lung Carcinoma (SCLC)[21]

Small Cell Lung Carcinoma (SCLC), which is caused by smoking and spreads more quickly than Non-Small Cell Lung Cancer (NSCLC), which grows and spreads more slowly[22]. About 85% of cases are NSCLC, which is further divided into 3 types:

- Large cell carcinoma,
- Squamous cell carcinoma, and
- Adenocarcinoma[23].

The most common kind of lung cancer, Adenocarcinoma, has a poor prognosis. Additionally, lung cancer can be histologically divided into 2 main types:

- Neuroendocrine cell-derived SCLC, which accounts for 15-20% of all lung cancer patients, and
- Epithelial cell-derived NSCLC, which accounts for 80-85%[24].

3. Stages of Lung Cancer

The stages of lung cancer are crucial in determining the prognosis and treatment options for patients. Non-Small Cell Lung Cancer (NSCLC) is typically classified into stages I, IIA, IIB, III, and IV, while Small Cell Lung Cancer (SCLC) is classified into limited and extensive stages[25]. The 5-year survival rates vary significantly depending on the stage at diagnosis, with localized stage showing a 5-year survival rate of 63.7% in males and 84.3% in females, while the distant stage has a 5-year survival rate of 7.0% in males and 13.4% in females[26]. Early-stage lung cancer has a far higher survival rate, with approximately 70% or more 5-year survival rate, dropping to less than 10% for patients diagnosed at an advanced stage[27]. The Tumour Node Metastasis (TNM) staging system estimates the 5-year survival in NSCLC ranging from 73% in stage IA to 13% in stage IV disease. Furthermore, the 5-year survival rates drop from 60% for stage IIA to 36% for stage IIIA disease[28].

4. Risk Factors and Etiology

4.1 Smoking and Tobacco Exposure

Smoking and tobacco exposure has had extensive research carried out in this risk factor and is known to be a factor of significance in relation to lung cancer[29]. The poisonous substances found in environmental tobacco smoke significantly increase the likelihood of developing lung cancer. It has also been proven to reveal tobacco smoke in its active as well as passive modes as an important player in the etiology of lung cancer[30]. More research on the topic has revealed that the use of tobacco nicotine is carcinogenic and one of the known risk factors for lung cancer. In identifying that tobacco smoking has an effect on the sequence landscape of mutations, tobacco smoking causes in a person by suggesting that exposure to diverse chemical structures might affect what mutations tobacco smoking causes[31]. In addition, tobacco control is a crucial reducing the lung cancer burden.

4.2 Environmental and Occupational Exposures

Environmental and occupational exposures play a significant role in lung cancer overweight risks. Substantial evidence demonstrates high occupational exposure as an applicable risk for small cell lung cancer, and a joint effect with tobacco smoking increases the rate[32]. Apart from this, household air pollution comprising exposure to solid fuels for cooking or heating or stove and environmental tobacco smoke has been linked to an increased rate of new cases of lung cancer[33]. Asbestos, silica, and oil refinery exposure have been recognized as major risk factors for lung cancer, independent of tobacco smoke exposure. Further, third hand smoke, which refers to residual tobacco smoking pollutants other than the mainstream and side-stream smoke, may enhance development of lung adenocarcinoma[34]. Moreover, the exposure to PM2.5 in non-occupational air pollutions is known to induce lung injuries, with an even more increased risk in lung cancer.

4.3 Genetic Predisposition and Familial Risk Factors

Genetic predisposition and familial risk factors also contribute to the risk of developing lung cancer[35].

Family history (1st degree) has been identified as a significant risk factor for the occurrence of cancers of the lung and breast. Moreover, the identification of polymorphic cis-regulatory variants as the lung carcinogenesis risk markers also showed the effect of various chemotherapy regimens on the overall survival of the lung cancer patients[36].

5. Diagnosis and Staging

Various clinical presentations, imaging modalities, biopsy techniques, molecular testing, and staging processes are used in the diagnosis and staging of lung cancer. Imaging techniques that play a major role in the diagnosis and staging of lung cancer are PET-CT[37]. Moreover, a few limitations of classic imaging technologies, such as radiography, CT, and MRI, stimulated studies of new imaging methods for obtaining better characterization of tumours and guidance for targeted therapy. Artificial intelligence has achieved considerable diagnostic accuracy in CT imaging for the diagnosis of lung cancer, with great value in the clinical diagnosis of lung cancer, as well[38]. Besides, the system of TNM staging to be considered in relation to prognosis and as a guide in therapeutics has great importance.

Biopsy is useful in obtaining tissue specimen for molecular testing and biomarker analysis; thus, it may take the form of bronchoscopy, needle biopsy, or surgical biopsy. Molecular testing- diagnosis, and prognosis of SCLC: The serum biomarkers, such as TuM2-PK, NSE, and ProGRP, are diagnostic and prognostic biomarkers of SCLC cases[39]. Nowadays, liquid biopsy has been considered a novel strategy for treatment of lung cancer because it is non-invasive and can be used to perform liquid biopsy and pathology assessment[40].

This gives the TNM staging, which is important to provide the spread of the tumour and be able to stir the prognosis among treatment options. Identification of changes in levels of biomarkers, such as CEA and ProGRP, in fluid of single lung bronchus bronchoalveolar lavage aids in localizing, diagnosis, and staging lung cancer[41]. Its overall survival reduction post smoking cessation among NSCLC patients is also important in the discovery of new biomarkers and patient selection in upcoming therapeutics[14].

Outside the context of the COVID-19 pandemic, weight loss has been attributed to the first diagnosis of lung cancer in a great proportion of patients, hence at a very advanced stage of the disease at the time of presentation[42]. In addition, the effects the COVID-19 pandemic has had on the diagnosis of lung cancer have caused delayed cases and one could expect an increase in the disease burden.

6. Treatment Modalities

The modalities of cancer treatment vary widely and include surgery, chemotherapy, radiation, targeted therapy, immunotherapy, and emerging modality according to clinical trials[43]. Surgery means a lot of various resections, with minimally invasive techniques like robotic surgery and Video-Assisted Thoracoscopic Surgery (VATS), which have played a very big role in giving the best results to the patient, including lobectomy, segmentectomy, and pneumonectomy[44]. Chemotherapy regimens include platinum, taxanes, and vinca alkaloids used either neoadjuvantly or adjuvantly. Radiation therapy can be performed as external beam radiation or Stereotactic Body Radiation Therapy (SBRT), which may be used combined or adjuvant[45]. Targeted therapy would include Epidermal Growth Factor Receptor (EGFR) inhibitors, ALK inhibitors, ROS1 inhibitors, BRAF inhibitors; meanwhile, immunotherapies would include Programmed cell Death protein 1 (PD-1) inhibitors, Programmed Death-Ligand 1 (PD-L1) inhibitors, or combination therapy[46].

Immunotherapy has emerged as one of the serious and effective therapeutic modalities for the management of lung cancer, particularly non-small cell lung cancer[47]. It has represented standard treatment for lung cancer, while most research focused on the reactivation of immune cells in order to kill the tumour. In addition, it has been reported that immunotherapy showed interesting results in the treatment of lung cancer and may have an advantage in overcoming resistance and improving treatment by targeting the tumour microenvironment[48]. Moreover, the immune composition of the tumour microenvironment is a known predictor of immunotherapy response, but the role in responsiveness to surgery or chemo-radiation has not been explored[49].

The role of immunotherapy in lung cancer is buttressed by the food and drug administration's approval of the first Immune Checkpoint Inhibitors

(ICIs) for lung cancer therapy in 2015[50]. Regrettably, some lung cancers could be immunotherapy-resistant. All the same, in the last decade, the improvement in lung cancer survival has been remarkable, complementing gains in targeted therapy[51].

7. Multidisciplinary Approach and Personalized Medicine

A multidisciplinary care approach, which involves surgery, medical and radiation oncology, and palliative care, plays an important role in this connection, supported by key organizations like the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society[52]. Ideally, palliative care in outpatient multidisciplinary clinics is integrated and already particularly useful in patients undergoing radiation therapy or chemotherapy[53]. Molecular profiling and biomarker-driven therapies are therefore pivotal in personalized medicine for lung cancer, assisting the individualized estimation of risk and treatment strategies. A consensus on the treatment of NSCLC states that the aspects of comprehensive multidisciplinary care and individualized therapy are playing an increasing role in determining patient prognosis[54].

Multidisciplinary care in lung cancer is important for transparency and shared decision-making. Although evidence in support of this is limited in particular for community health care settings, it is also essential for the stage III NSCLC patient with an emphasis on effective communication[55]. The SARS-Cov2 pandemic has posed challenges to multidisciplinary lung cancer care, urgent adaptable and patient-cantered approaches[56]. Creation of programs dedicated to lung nodule management with the integration of advanced technology and patient navigation to offer standardized services to patients and referring physicians[57].

8. Management of Complications and Palliative Care

Adequate care in the management of complications in lung cancer consists of treating the associated symptoms, which include pain, dyspnea, and cough, and the prescription of supportive and palliative treatment, and advance directives. Cough is an unpleasant symptom and can be controlled by mobile technologies and the occurrence of acute health deterioration[58]. This is the most common complication postoperatively, and, along with anorexia and fatigue, can significantly impact the quality of life. It can be better managed with treatments. Dyspnea is mainly caused by VTE and should be treated. Preoperative assessors, for example, fractional exhaled nitric oxide, might predict postoperative cough-related quality of life, and therefore the optimization of the management of Dyspnea should be started timely. This is more so during this COVID-19 era, in regards to early diagnosis in relation to pain management and overall care[59].

Nutritional and psychosocial supportive care interventions form a part of palliative care in lung cancer patients. Although not from the literature on lung cancer, studies in patients with refractory or unexplained chronic cough are important to note because this literature shows the critical need to understand and effectively manage cough reflex hypersensitivity, which can be a significant problem with lung cancer patients who will need supportive care interventions[60].

End-of-life care and advance directives are essential facets in the management of complications and palliation in lung cancer patients. However, a study on patient's expectations before and after therapy, although outside the realm of end-of-life issues, emphasizes patients rights in disease management, an issue related to advance directives and end-of-life care[61].

9. Future Directions and Challenges

Tremendous advances in lung cancer research have been made in recent times with respect to early detection, biomarker testing, and risk prediction[62]. However, many challenges still remain, such as the management of idiopathic pulmonary fibrosis comorbidities in patients, the impact of the COVID-19 pandemic on lung cancer treatment, and how to achieve better outcomes for patients with non-small-cell lung cancer by means of innovative therapies such as antibody-drug conjugates and nanomedicines[63]. Moreover, overcoming the therapeutic resistance like cisplatin resistance is still a crucial issue in clinical tumour therapy. Besides, there still are challenges in the staging of pathologists on early-stage lung Adenocarcinoma[64].

9.1 Drugs Used in Treatment of Lungs Cancer

Lung cancer is a complicated disease, and multiple therapies are currently in use, including surgery, chemotherapy, immunotherapy, targeted therapy, and more steps, which keep innovation. It can hence be said that recent challenges no place an added urgency on strategies to be clenching towards curing or managing lung cancer in particular, especially with reference to late-stage cancers[43]. Immunotherapy is, indeed, effective for the treatment of lung cancer, capable of overcoming immune resistance and enhancing the targeting of the tumour microenvironment[49]. In addition, Chinese Herbal Medicine (CHM) therapy, when integrated as part of the standard therapy regimen, has been noted to reduce the risks of mortality in patients with stage IV lung cancer[65].

Also, development of novel drugs and therapies targeting some selective molecular pathways as well as cellular functions are undergoing research nowadays. For instance, exosomal miR-196a-5p has been shown in lung cancer cells to be involved in the development of radio resistance with the potential of targeted actions at the molecular level[66]. On the other hand, the development of nanomedicine, a more or less novel regime for the therapy of lung cancer, could also be an incentive for the creation of a targeted delivery system in the attempt to lower systemic exposure, distribution, and, most importantly, drug-related toxicity[63].

Additionally, major driver gene identification and targeted therapy revolutionized therapeutic landscapes for non-small-cell lung cancer and showed better efficacy compared to traditional chemotherapy[67]. Discoveries improve treatment modes and continue developing new target drugs, such as antibody-drug conjugates, and now they have expanded the range of possible patients who are to screen positive for driver genes in relation to NSCLC[68].

Not to mention targeted therapy, advanced staging treatment NSCLC is a historical milestone with the change of the immunotherapy position that rewrites the treatment pattern of lung cancer. The improved immunotherapeutic effects by using a tumour cell vaccine together with Newcastle disease virus in the treatment in lung cancer cases have seen tumour growth inhibition to be significantly increased[69].

9.2 Advances in Lung Cancer Prevention

Inhibition of lung cancer has been assessed through various methods such as vaccine development, dietary interventions, environmental determinants, and screening strategies. Prophylactic approaches on multipeptide vaccines specific to common EGFR mutations, for example, have been demonstrated to reduce lung tumorigenesis[70]. Thus, inhibition of lung metastasis has been demonstrated by the engineered nasal nano-vaccine[71]. These works give credence to the possibility of vaccines in the prevention of lung cancer.

Dietary manipulations have also been considered apart from vaccines. Reported that the chemopreventive potential of dietary phytochemicals against tobacco-associated lung carcinogenesis[72]. A strong association of low-fat dairy products intake with a decrease in risk of lung cancer, indicating a possible preventive option by changing dietary habits was also reported.

Even environmental determinants like the air pollution have been studied in relation to prevention of lung cancer that continues to emphasize the importance of early screening to prevent lung cancer and lower down the occurrence[73]. Further, it has put more emphasis on the influence that referral to palliative care may have at the end of the day, which is possibly preventing emergency visits of lung cancer patients[74]. These findings continue to underscore the importance of early detection and treatment in the prevention of lung cancer.

Screening strategies, including LDCT and comprehensive cancer screening, have shown promise to reduce lung cancer mortality. The National Lung Screening Trial provided evidence that LDCT-based screenings reduced lung cancer deaths by about 20% relative to chest radiography in a high-risk population[75], also discussed the potential of comprehensive cancer screening centers in detecting lung cancer and other malignancies[76].

9.3 Comorbidities of Lung Cancer

This is a complicated disease associated with a large number of comorbidities that belong to a group of diseases and substantially influence the disease outcome. Comorbidities that usually occur with lung cancer are the following: COPD, ILD, IPF, and their various combinations together[77]. Such comorbidity might impair the prognosis for lung cancer and raise the healthcare

costs. In addition, comorbidities have been associated with delays in treatment, increased surgical risk, and inferior short-term results after surgery[78]. Moreover, there has been an observation that comorbidity has a positive association with non adherence to lung cancer screening, hence delaying diagnosis and poorer outcomes. The overall comorbidities prevalence in lung cancer is huge, and as reported in one study, its weighted average prevalence is 33.4%, with lung cancer being among the cancers that have the high prevalence of comorbidities prevalence in respect to other cancer types[79].

In addition, it has shown appreciable effects on the role of comorbidities in patients survival with lung cancer, such as its prevalent comorbidities having even exerted an adverse effect on patients survival. This is further reinforced by the observation that comorbidities often are associated with a poor prognosis in patients with cancer[80].

Lung cancer is further complicated by comorbidities such as COPD and ILD. These comorbidities relate to events, like pulmonary Cachexia and Sarcopenia, making management a hard task. There is no standard protocol offered in patients with comorbid ILD and lung cancer, hence compounding the situation[81]. Lung cancer patients with comorbidities are also at increased risk of thromboembolism, especially with treatment[82]. In a study finding links of current cancers, chosen a priori including lung cancer, with emphatic evidence, it underpins the importance of understanding the effect of comorbidities on current infectious diseases[83].

9.4 Covid 19 Impact on Lung Cancer

The impact of COVID-19 on lung cancer patients has been seen in different countries and caring facilities. An example includes a study in China, to find that earliest to the outbreak, COVID-19 affects the survival of the uninfected patients of advanced Non-Small Cell Lung Cancer (NSCLC) under the use of chemotherapy[84]. Other studies evaluating how the COVID-19 pandemic affected the primary lung cancer screening program came from Japan, where the rate of aging in the population is among the highest worldwide[85]. The studies targeted the diversity of ways in which COVID-19 impacted lung cancer care, from topics on diagnosis to screening programs.

Moreover, the treatment and care for lung cancer have also shown some delay during the pandemic, which resulted in the incredible growth of tumour volume in Greece and high mortality in Japan, yet without a single patient being subjected to surgery[86,87]. Such a situation leads patients with the diagnosis of lung cancer to have limited access to timely care. There is also research that shows delayed diagnosis and treatment in Italy and Brazil, and questions about the availability of curative options. The related molecular research identified substances and genes that interact with both lung cancer and COVID-19, which reemphasize the importance of targeted therapies[88].

9.5 Other Organ Affected Due to Lung Cancer

Lung cancer metastasis to primary organs has been broadly studied well by the availability and prognosis. Metastasis to primary organs pinpoints the systemic nature of the lung cancer disease and to transfer through all over the body parts their[89].

In addition, the interrelations in lung-intestinal microecology were a therapeutic factor in lung cancer, which demonstrated that the influence of the intestinal microenvironment on the human body could lead to it or to the occurrence and development of or the therapy for lung cancer. Intestinal flora can influence the development and metastasis of lung cancer, and multi organs work together in this disease[90].

In addition, studies performed on primary graft dysfunction indicate that lung allograft recipients have fewer chances of survival, primarily due to the development of primary graft dysfunction, which has clinical significance in a large proportion of lung recipients. This again underscores the impact of lung cancer on the transplanted organ and, therefore, the problems that lung transplantation brings in the setting of this disease to a larger extent[91].

In addition, the influence of other metastatic organ sites on the prognosis of Non-Small Cell Lung Cancer (NSCLC) has been touched upon; probably, it is significant in determining the spread of lung cancer to other organs and has further effects on the patient outcome[92].

An inquiry has been made on mental health and psychological well-being in relation to lung cancer, with some studies actually delving into the reason for estimates of suicidal ideations among lung cancer patients. This highlights how far-reaching the effects

of lung cancer go beyond the physical aspects to cover mental and emotional well-being[93].

Besides, reports also state that the possibility of such lung cancer to metastasize to the kidney also cannot be ignored, thereby signifying how many and in how many different organs the metastasize of lung cancer can take place. And thereby, it further dictates the requirements of a regular follow-up and look for this possible metastasize of this lung cancer to the different parts of the body[94].

9.6 Complications from the Treatment of Lung Cancer

Lung cancer treatment is done *via* methods like radiotherapy, chemotherapy, surgical resection, and immunotherapy. These treatments, however, are known to be fraught with a plethora of complications and side effects. In general, radiotherapy is going to lead to the partial loss of lung function and complications, such as lung problems induced by radiation[95]. In contrast, surgical trauma and anaesthesia during thoracoscopic surgery for lung cancer can lead to limited cough ability, lung infections, and many other postoperative complications[96]. Importantly, chemotherapy drugs are quite toxic, and their side effects can become quite disabling, whereas in certain subsets of patients, they may even precipitate acute respiratory distress syndrome[97]. Complications in the form of chylous effusions and chylopericardial tamponade have been observed postoperatively in lung cancer patients undergoing lobectomy and lymphadenectomy but are extremely rare[98].

Moreover, when lung transplantation is performed for lung malignancies, a significantly large proportion of these patients can develop chronic lung allograft dysfunction, which ultimately impacts long-term survival[99]. In addition, the occurrence of lung cancer concomitant with COPD increases the rate of postoperative complications in the event of surgical resection in lung cancer. It is worth noting that recent COVID-19 infection can also influence the outcome of thoracoscopic lobectomy of lung cancer, owing to the upstaging to a pathological condition because of delays in the surgical treatment[100].

Advances in the treatment for lung cancer have paved the way for immunotherapy to be a significant therapeutic modality. The pathogenesis of lung cancer is still a puzzle and is the primary hindrance to developing effective treatment. Besides, the management of the side effects, including radiation-induced lung injury and related immune adverse events, has become highly complicated[95], which underlines the importance of giving priority to the treatment of lung cancer and mapping the therapy response to ensure improved patient outcomes.

10. Potential of Natural Remedies in the Management of Lung Cancer

In consideration of the significant worldwide impact of lung cancer and the difficulties associated with traditional therapies, there is an increasing interest in investigating natural remedies and bioactive natural materials for the prevention, treatment, and supportive care of lung cancer. Nature provided a vast array of medicinal plants, herbs, fungi, minerals, and other natural resources, many of which have anticancer potential *via* diverse pathways.

The vebioside, derived from *Thevetia peruviana*, was tested on A549 and H460 lung cancer cell lines as well as in orthotopic mouse models. It exerted its antitumor effects by inhibiting the phosphoinositide 3-kinase - protein kinase B (PI3K-AKT) signalling pathway, a crucial route often involved in cancer cell survival and proliferation[101]. Thymol, derived from *Satureja thymbra* and *Ocimum gratissimum*, has been shown to induce cell cycle arrest and apoptosis in NSCLC cells particularly A549 and KLN205 cell lines *in vitro* studies. This indicates that it has the ability to naturally cause an alteration to the cell cycle and induce apoptosis[102]. Similarly, *in vitro* (A549, HCC827, PC9 cell lines) and *in vivo* (C57BL/6 mice) studies using ginseng-derived ginsenoside Rg3 showed a beneficial effect as an adjunct therapy through the activation of the VRK1/P53 pathway which initiated tumour suppression and decreased therapeutic resistance[103]. Cinnamaldehyde source from *Cinnamomum cassia* displayed extensive anticancer actions in many NSCLC cell lines as well as animal experiments. It inhibited Wnt/β-catenin signalling, decreased matrix metalloproteinases MMP-2 and -9, and blocked cell cycle which in turn inhibited cell proliferation and metastasis[104]. Sesamin obtained from *Sesamum indicum* affects AKT/P53 signalling and promotes ROS and cell death in NSCLC models through

mitochondrial damage[105]. Eupatolide, derived from *Inula helenium*, was anticancer by inhibiting the Signal Transducer and Activator of Transcription 3 (STAT3) signalling pathway in A549 and H1975 cells and in BALB/C mice. The STAT3 pathway is a major regulator of cancer progression, and inhibition of STAT3 can result in tumour regression[106]. Piperlongumine, from the plant *Piper longum*, was shown to be effective against A549 and NCI-H460 cell lines and in animal studies, by inhibiting the NF-κB pathway, inhibiting Profilin-1 (PFN1), and blocking STAT3 to induce apoptosis and inhibit tumour migration[107]. Jervine, a steroid alkaloid from *Veratrum* rhizome, also showed potent anti-NSCLC activity. It suppressed the AKT/mTOR and hedgehog signalling pathways and promoted autophagy-related apoptosis in A549 and H1299 cells and in nude mice[108]. Meanwhile, Ophiopogon saponin C1, from *Liriope muscari*, was found to block the cell cycle in A549 cells and reduce tumour growth in mice, suggesting its role in halting cancer cell division[109]. Kaempferol, a flavonoid in cruciferous vegetables, inhibited the Nrf-2 signalling pathway in A549 and NCI-H460 cells. Since Nrf-2 is involved in antioxidant defence and cell survival, down-regulating this factor is a mechanism to reduce tumour viability[110]. Finally, Cordycepin, which is derived from *Cordyceps sinensis*, acted in both cell lines and mice *via* modulation of the VEGF/PI3K/AKT signalling pathway, contributing to anti-angiogenic and pro-apoptotic effects[111].

11.1 Nutritional and Dietary Interventions

As shown in Table 1, high intake of fruits, non-starchy vegetables, and specific phytochemicals may reduce lung cancer risk, while red or processed meats are associated with increased risk.

11.2 Traditional and Complementary Medicine Approaches

11.2.1 Ayurveda

This ancient system from India emphasizes the balance among body systems and utilizes herbs including *Curcuma longa* (turmeric) and *Withania somnifera* (*Ashwagandha*). Turmeric contains curcumin, a compound with anti-inflammatory and anticancer properties, while *W. somnifera* is recognized for its immunomodulatory effects. In lung cancer studies, these herbs have been examined for their use to induce apoptosis and inhibit proliferation[114].

11.2.2 Traditional Chinese Medicine (TCM)

TCM is based on herbal formulas for treating lung cancer, as TCM approaches the treatment of lung cancer

Table 1. Dietary and supplement interventions for lung cancer[112,113]

Category	Recommended	To Avoid
Foods	Fruits Non-starchy vegetables (leafy greens, tubers, carrots) Foods high in carotenoids (carrots, sweet potatoes, spinach, *etc.*) Foods high in selenium (Brazil nuts, tuna, salmon, mushrooms, eggs, barley, grass-fed beef, turkey) Foods rich in quercetin (capers, dill, kale, buckwheat, sweet potatoes, apples) Green tea Spices: Turmeric, black cumin Soy Garlic Pomegranate	Red meat Processed meat High glycemic index diets
Supplements	Astragalus Omega-3 (EPA: DHA ≥4:1) Curcumin Ginseng Sun soup Melatonin Vitamin D (early-stage NSCLC) Probiotics	Selenium (excessive) Vitamin A β-carotene VitaminD (advanced-stage NSCLC)

by balancing the body and strengthening the body's defences against disease. Based on extensive research of herbs with immunomodulatory and anticancer properties, various herbs such as, *Panax ginseng* has been recommended for lung cancer treatment. Research has documented how TCM formulations may provoke cell death even in treated lung cancer cells, indicating TCM formulations may reverse therapeutic resistance. TCM formulations may also modulate the adaptive, as well as the innate immune responses in lung cancer patients[115].

11.2.3 Siddha and Unani Systems

Practiced predominantly in South Asia, these systems also employ various herbs for managing respiratory ailments and tumours. For instance, *Ocimum gratissimum* (*Rama Tulasi*) is used in *Siddha* medicine for its potential to induce apoptosis in lung adenocarcinoma cells[116].

11.3 Bioactive Compounds and Phytochemicals

Numerous studies have identified bioactive compounds in natural products that can inhibit cancer cell growth, modulate signalling pathways, and enhance the efficacy of standard treatments. The primary mechanism of action of plant secondary metabolites, which are thought to be safe and beneficial in the treatment of cancer, is the regulation of several signalling pathways[117]. Alkaloids, phenolics, sulfur-containing compounds, and terpenoids are some of the four general categories into which phytochemicals can be divided[118].

11.3.1 Alkaloids

Alkaloids, a diverse class of naturally occurring nitrogen-containing compounds, have demonstrated significant anticancer potential in lung cancer research[119]. Notably, acutiaporberine has been shown to induce apoptosis in lung cancer cells, highlighting its promise as a pro-apoptotic agent[120]. Similarly, beta-carboline alkaloids have exhibited cytotoxic activity through the modulation of critical signalling pathways, including ERK1/2 and Akt/mTOR, thereby inhibiting tumour cell proliferation[121]. Berberine, another well-studied alkaloid, has been reported to suppress tumour cell growth and promote apoptosis by regulating the expression of pro-apoptotic proteins such as Bax and the executioner caspase-3[122]. Evodiamine enhances the host immune response against lung tumours by reducing the expression of MUC1-C and PD-L1, concurrently increasing the infiltration of cytotoxic CD8+ T lymphocytes[123]. Furthermore, homoharringtonine has demonstrated the ability to inhibit tumour growth and metastasis by down regulating key oncogenic signalling pathways, including JAK1/STAT3 and KRAS/ERK/Akt/STAT3[124]. Indole-3-carbinol has been shown to elevate oxidative stress levels within lung cancer cells, resulting in increased apoptotic activity[125]. Collectively, these findings underscore the therapeutic potential of alkaloids as multi-targeted agents in the management of lung cancer.

11.3.2 Phenolics

Phenolic compounds, known for their antioxidant and anti-inflammatory properties, have also shown promising anticancer activities in lung cancer models[118]. Acacetin has been reported to significantly decrease tumour cell viability, invasion, and migration by suppressing the p38α MAPK pathway, thereby reducing cancer progression[126]. Apocynin has demonstrated the ability to inhibit tumour growth and invasion as well as disrupt the microtubule network in lung cancer cells and xenograft models, suggesting a multifaceted mechanism of action[127]. Baicalein, another notable phenolic compound, has been shown to reduce tumour metastasis and invasion through the inhibition of S-nitrosylation of ezrin, an actin binding protein involved in cell motility and structural integrity[128]. Cardamonin has been observed to suppress tumour growth and metastasis by modulating the PI3K/Akt/mTOR pathway, a crucial signalling cascade in cancer development and survival[129]. Additionally, curcumin has exhibited multiple anticancer mechanisms in lung cancer cells, including the induction of apoptosis, cell cycle arrest, and DNA damage, further underscoring the potential of phenolic compounds as adjunctive or alternative therapeutic options in lung cancer management[118].

11.3.3 Sulfur-containing Compounds

Among sulfur-containing compounds with anticancer potential, allicin and sulforaphane have garnered considerable attention in lung cancer research. Allicin has demonstrated the ability to overcome cisplatin

resistance in lung cancer cells by inhibiting hypoxia-mediated pathways, thereby restoring chemo sensitivity and enhancing therapeutic efficacy. Sulforaphane, a compound derived from cruciferous vegetables, has been shown to suppress tumour growth by inducing G2/M cell cycle arrest, which limits cancer cell proliferation. Furthermore, sulforaphane modulates epigenetic mechanisms, suggesting its ability to reprogram cancer cell gene expression and support sustained anticancer activity. Collectively, these findings highlight the promise of sulfur-containing natural compounds in overcoming therapeutic resistance and modulating critical signalling and epigenetic pathways in lung cancer therapy[118].

11.3.4 Terpenoids

Natural compounds such as dihydroartemisinin, ursolic acid, and withaferin A have exhibited significant anticancer potential in lung cancer[130]. Dihydroartemisinin induces cell cycle arrest and apoptosis by modulating the p38 MAPK pathway[131]. Ursolic acid inhibits tumour growth, angiogenesis, and metastasis by inducing autophagy and suppressing the Akt/mTOR signalling pathway. Withaferin A increases oxidative stress and reduces cell viability in lung cancer cells[118]. These findings highlight their potential as effective natural agents in lung cancer therapy.

11.4 Research and Future Perspectives

Natural compounds derived from medicinal plants are gaining increasing attention as promising alternatives to conventional therapies for lung cancer due to their multitarget mechanisms[132]. Phytochemicals such as curcumin, baicalein, gingerol, and caffeic acid have demonstrated their ability to modulate key signalling pathways often dysregulated in lung cancer, including PI3K/Akt/mTOR, JAK/STAT, and MAPK pathways. A major innovation in this field is the use of green-synthesized metallic nanoparticles-crafted using plant-based secondary metabolites like flavonoids and alkaloids- which have shown improved bioavailability, targeted delivery, and reduced systemic toxicity[133]. For instance, nanoparticles composed of silver, gold, zinc oxide, and selenium derived from plants such as *Moringa oleifera*, *Punica granatum*, and *Zanthoxylum rhetsa* have displayed potent cytotoxic effects against lung cancer cell lines.

Specifically, *M. oleifera* has emerged as a significant candidate in lung cancer therapy, with caffeic acid from this plant showing high binding affinity toward EGFR and stability in molecular dynamics simulations[134]. Future research is increasingly focused on enhancing the solubility, stability, and tumour-specificity of these natural agents through nano formulation strategies. Integration of computational tools like molecular docking, bioinformatics, and systems biology is deepening our understanding of compound-target networks and helping identify key regulatory nodes in cancer progression[133]. Moreover, addressing Multitherapeutic Resistance (MDR) - a major obstacle in treatment- is another promising avenue, with agents such as quercetin, kaempferol, and baicalin showing potential to counteract resistance mechanisms[132].

Despite these advances, the clinical translation of natural compounds remains limited. Few phytochemicals, such as curcumin and baicalin, have reached clinical trial phases, underscoring the need for intensified translational research. Combinations of plant-derived compounds with modern therapies-like chemotherapy and immunotherapy - are being explored to boost treatment efficacy while minimizing adverse effects[132]. Computational modelling has further suggested that several phytochemicals can influence multiple hallmarks of lung cancer, such as apoptosis induction, angiogenesis inhibition, and immune system modulation. Preclinical studies with plant extracts such as *Annona muricata* and *Camellia sinensis* have supported their anti-cancer activity, reinforcing their drug development potential[132].

The involvement of non-coding RNAs, especially miRNAs, in lung cancer signalling and their modulation by phytochemicals is another area gaining momentum. Traditional medicine systems from Chinese and Indian heritage continue to be rich reservoirs of anti-cancer agents, and their integration into modern oncology is becoming increasingly systematic. However, researchers stress the importance of standardization, quality control, and rigorous clinical validation to ensure reproducibility and safety[135]. Efforts are underway to improve nano-biocompatibility and pharmacokinetics through techniques such as surface modifications and ligand-conjugation[133]. There is also a growing shift towards eco-friendly and sustainable synthesis methods using renewable plant sources[132].

Looking ahead, the advancement of lung cancer therapeutics using natural compounds will depend heavily on integrated omics platforms- genomics, proteomics, and metabolomics- to identify responsive biomarkers and tailor personalized medicine approaches. The role of the gut microbiota in modulating the effectiveness of phytochemicals is another emerging area of interest[135]. Ultimately, collaborative research across the domains of pharmacognosy, nanotechnology, molecular biology, and oncology is essential to harness the full potential of natural compounds in the treatment of lung cancer.

12. Conclusion

Lung cancer remains a formidable global health challenge, characterized by high morbidity and mortality despite advancements in diagnostic modalities, precision therapies, and immunotherapeutic strategies. However, treatment resistance, recurrence, and significant treatment-related toxicities continue to pose obstacles to effective disease management. The growing interest in natural remedies and bioactive natural compounds has unveiled a promising avenue for lung cancer prevention and therapy. Alkaloids, phenolic compounds, sulfur-containing derivatives, and terpenoids sourced from nature have demonstrated potent anticancer activities through various mechanisms, including apoptosis induction, cell cycle arrest, immunomodulation, and the regulation of key oncogenic signaling pathways. Furthermore, traditional medical systems such as *Ayurveda*, Traditional Chinese Medicine, *Siddha*, and *Unani* offer a wealth of natural formulations and herbal extracts with established historical use and emerging evidence of efficacy in preclinical lung cancer models. These natural agents not only exhibit multifaceted mechanisms of action but also hold potential for integration into existing treatment regimens, either as adjunctive or complementary strategies to improve therapeutic outcomes and reduce adverse effects. Future research must prioritize the clinical validation of these natural remedies, elucidate their pharmacokinetic and pharmacodynamic profiles, and establish standardized dosing protocols to ensure their safe and effective incorporation into lung cancer management paradigms. Such integrative approaches hold promise for addressing the complex pathophysiology of lung cancer and enhancing the holistic care of affected patients.

13. Author Contribution

Conceptualization, R.S. and P.S.B.; Literature search and data collection, N.H. and P.P.; Writing- original draft preparation, R.S. and N.H.; Writing- review and editing, R.S., P.S.B., and M.P.; Supervision, R.S. and M.P.; Visualization, N.H. and P.P. All authors have read and agreed to the published version of the manuscript.

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