# *Review of Literature*

# CHAPTER NO 2: REVIEW OF LITERATURE

Especially in the past decade, when there has been a greater emphasis placed on research into natural therapies, plant life has been recognized as a rich source of natural products that are beneficial to human health maintenance. In recent years, there has been a rise in the pharmaceutical industry in India in the use of various us plant-based compounds. The World Health Organization believes that the best place to obtain a wide variety of drugs would be from the plants that are used for medicinal purposes. Around eighty percent of people living in developed countries make use of traditional medicine. Traditional medicine typically contains compounds that are derived from medicinal plants. As a result, such plants need to be researched in order to gain a better understanding of their qualities, including their reliability and productivity [46]. The National Cancer Institute has evaluated approximately 114,000 plant extracts for their potential to fight cancer after collecting approximately 35,000 plant samples from 20 different countries [47]. It is possible that the use of plant extracts and phytochemicals, both of which are known to have anticancer (lung carcinogenesis) properties, could be of great significance in the treatment of various conditions. Over the course of the past few years, researchers from a variety of nations have carried out a variety of studies to demonstrate that such efficiency [48].

LC is a deadly disease that develops in the bronchi. Death from LC exceeds all other cancers combined as the main cause of cancer-related fatalities globally. Even while smokers have a higher chance of developing LC than nonsmokers do, LC may happen to anybody at any time. Smoking for a long period and smoking a lot of cigarettes raises your chance of LC. However if you've been a smoker for a long time, quitting may greatly lessen your risk of getting LC. Among malignant neoplasms, LC is by far the most prevalent worldwide. Cancer is the top cause of mortality for both men and women worldwide, and this disease is a major contributor. Since tobacco smoking is the leading cause of lung cancer, it is also the key determinant of demographic trends in LC rate and death over time. Tobacco usage is also a major factor in LC death incidence. The clinical epidemiology of LC may be influenced either only by tobacco use or in combination with other variables such as genetic vulnerability, poor nutrition, environmental effects, and air quality. As a corollary, recent advances in the molecular

categorization of LC have started to shed light on its origin, especially in never-smokers. The link between LC and tobacco usage makes this point more poignant. Smoking tobacco has been effectively separated as the fundamental cause in the formation of LC; nonetheless, despite this, LC remains the highly common and deadly kinds of cancer worldwide. Tobacco substances other than cigarettes should be the centre of upcoming tumor control initiatives and investigation, as well as a deeper knowledge of the mechanisms that contribute to the onset of LC in never-smokers [49]. Developers discuss the molecular pathogenesis of LC, which involves mutations in both dominant oncogenes and the necessary recessive tumour suppressor genes, in addition to modifications in signal transduction, death of cells, autophagy and peripheral immune growth expansionary loops, angiogenesis, and host immune responses. Lung growth and differentiation, in addition to the multistep carcinogenic practice called as preneoplastic lesions, are related to these changes. New techniques for the initial diagnosis, remediation, recovery, and outcome of LC are discussed, as are their translational functionalities [50]. The treatment of NSCLC has come a long way in the last 20 years, In addition to advancing initial diagnosis and multidimensional treatment; these developments also have expanded our knowledge of the disease's genetics and the frameworks that push tumour growth. When immunotherapy is used in conjunction with molecular kinase inhibitors, survival percentages have increased dramatically for some cases. However, ultimate healing and survival chances for NSCLC remain extremely poor, especially in situations of metastatic illness. Therefore, continued development into novel medications in addition to mixed therapy is necessary to expand the therapeutic advantage to a broader participant group and to enhance conditions in NSCLC [51].

## 2.1. OVERVIEW OF LUNG CANCER

Cancer is genetic disorder that can be caused by either genetic or epigenetic alterations in the somatic cells. It is characterized by abnormal cell growth, which can spread to other areas of the body. There were 18 million new cases of cancer diagnosed around the world in 2018, with 9.5 million new cases diagnosed in men and 8.5 million new cases diagnosed in women. Additionally, there were 9.6 deaths attributed to cancer in 2018. Prostate, lung, stomach, colorectal, and non-melanoma skin malignancies are the cancers that spread the fastest across the globe; however, there are more than one hundred different types of cancer that can affect humans. The effects of cancer are becoming significantly more severe on a daily basis. Tobacco

use is responsible for 22 percent of all cancers, while infections such as HIV, hepatitis b, and Epstein-Barr virus are responsible for 15 percent of all cancers, and a poor diet, obesity, excessive consumption of alcohol, exposure to ionizing radiation, and other factors are responsible for 10 percent of all cancers. In this review article, we make an effort to shed light on a variety of factors that can cause cancer, including the types of cancer, how cancer begins, signs and symptoms of cancer, tests used to diagnose cancer, treatments for cancer, and complications that can arise from cancer treatments. These days, a significant amount of effort is being put into the study of precision medicine in the hopes of making cancer treatment in the future more effective. Patients typically receive one or more of the following treatments: chemotherapy, radiation therapy, immunotherapy, surgery, hormone therapy, or combination treatments consisting of these treatments. The transplantation of stem cells is another excellent treatment for cancer; however, it is administered after the more conventional treatments have failed to stop the patient's bleeding sufficiently and restore their health [52].

**Redondo-Sánchez et al.** [53] studied the information of demographic inequality in significantly diverse LC results has gathered over the past decade. To learn more about how societal and economical variables affect LC worldwide, an assessment of existing studies was conducted. Author looked through four datasets for comprehensive studies that discussed the correlation between SES indicators and LC consequences. Both diagnostic and therapeutic results were considered. The selected comprehensive studies were evaluated for adequacy using AMSTAR-2. Eight separate assessments relied on data from 220 original investigations. Low-income people seem to be at increased chance for acquiring LC and suffering from the illness than higher-income people do. For the same reasons that individuals of poorer economic and social condition possess a lesser possibility of surviving melanoma than those of better economic and social, those of lower socioeconomic status also have a higher rate of comorbidities, are more likely to be hospitalised to the clinic as an urgent situation, and are less inclined to be both conventional and cutting-edge treatments. It seems that there may be demographic differences in the usage of LC screening, although this may alter if LC screening is more widely used. People of lower socioeconomic status tend not to get diagnoses until the illness has progressed further. Furthermore, this could alter if LC screening is more widely used.

**Eltayeb et al.** [54] proposed that most of the deaths from LC occur in developing countries and NSCLC account for almost all LC diagnoses. Inhibitors that specifically targeting the kinase region of EGFR are now being used in healthcare situations, and EGFR has evolved as a major targeted therapy in recent times for the diagnosis of individuals struggling from NSCLC. The processes and biological effects of lipid remodeling in malignancy have recently attracted more attention. This fascination is a modern phenomenon. Increases in lipid absorption, production, or oxidation, as well as lipid accumulation, have been linked to the development of several cancers, particularly in LC. Author summarise the role of metabolites in malignancy in this study. Specifically focussing in the link involving EGFR signalling and lipid metabolism remodeling to investigate its function in the initiation, development and therapy tolerance of LC. Further author present a short summary of pharmacological techniques that may address lipid metabolism in the diagnosis of LC.

**Chen et al.** [55] stated that immunotherapy has emerged in recent years as one of the most potentially fruitful approaches to the treatment of cancerous tumors. Nevertheless, immune activation that is not specific can potentially result in adverse effects related to immunotherapy (irAEs). IrAEs affect virtually every organ in the body and can pose a threat to life. On the other hand, there is not a lot of research being done on irAEs at the moment, and our knowledge of histopathology is lacking. This investigation is an inhibitor of "programmed cell death protein 1" (PD-1) was injected intraperitoneally into the investigative set of rats after the Lewis LC mouse model had been established. The "Hematoxylin and eosin" (HE), "Immuno Histo Chemistry" (IHC), and "Masson's trichrome" stains were utilized to examine the “pathological” features of the “heart, lungs, spleen, intestines, kidneys, and liver”. In order to assess how well the lungs were performing, echocardiography was used. The findings of investigation states that every organ tested positive for the presence of inflammatory cells in the “PD-1 inhibitor” group. Masson's trichrome staining confirmed that the “PD-1 inhibitor” group had more fibrosis of the heart, spleen, and kidneys than the control group. Also, the echocardiograms showed that the people using PD-1 inhibitors had worse heart function. Since the “PD-1 inhibitor” caused an inflammatory response, this may contribute to the impairment of several organs in the mouse model. This is the first study that takes a holistic approach to describing the pathological changes that are caused by PD-1 inhibitors in multiple organs.

**Kaya, et al.** [56] proposed the cancer continues to be one of the most common diseases and leading causes of death around the world. There are currently over 200 different types of cancer that have been identified. The early detection of cancer remains an essential component of effective cancer treatment. The identification of cancer biomarkers is an extremely important component of both the clinical diagnosis and the early treatment of cancer in patients. Cancers of the lung and colon are the most common types of disease. Despite this, they are a major cause of cancer-related deaths around the world because it is difficult to diagnose them in the early stages, which results in treatment being delayed. Cancerous tumors that originate in the colon frequently spread to the lungs. Nevertheless, locating biomarkers in the body, such as secretory proteins, is an intriguing method that shows promise for monitoring the progression of lung and colon cancer in patients at earlier stages. In today's world, a significant amount of effort has been invested in the discovery of biomarkers that, when combined with nanomaterials, can produce a sensor technology that is both sensitive and cost-effective for the non-invasive diagnosis of diseases. When it comes to the early diagnosis of lung and colon cancer, there are a great number of promising biomarker candidates that can be used. Some examples of these include DNA, RNA, mRNA, aptamers, metabolomics biomolecules, enzymes, and proteins. Electrochemical biosensors are gaining popularity as a method for detecting cancer markers due to their generally high sensitivity, ease of preparation, and speedy response times. Several electroanalytical methods are currently being developed for the detection of cancer biomarkers in the lung and colon. As a result, the most recent developments and enhancements in nanomaterials-based electrochemical biosensors for the detection of lung and colon cancer biomarkers are reviewed in this article. The time period covered is from 2011 to 2021.

**Xie et al.** [57] stated that LC is one of the most common types of cancerous tumors that endanger human life due to its high mortality rate and serious incidence rate. It is primarily subdivided into small cell LC and non-small cell LC (also abbreviated as NSCLC and SCLC, respectively) based on the histopathological characteristics (SCLC). NSCLC is responsible for approximately 80–85 percent of all cases of LC. In fact, LC metastasis is a common cause for therapy failure in medical participants. This is mainly due to the fact that our understanding of the processes that allow LC to metastasize to other organs is still limited. Several variables regulate the spread of LC cells. Among them include the "Epithelial Mesenchymal Transition" (EMT) conversion, blood vascular and lymphatic metastases, and the interplay

between different elements of the LC microclimate. As it turns out, the biochemical connections are far more intricate than we first imagined. Benchmark approaches for the establishment of curative medications may be improved with greater study into the processes of LC metastasis and the discovery for appropriate treatment targets. This investigation concentrates on the causes of LC metastasis and the links between these causes and the biological processes that underlie LC metastasis and the techniques that direct LC to certain organs. The major purpose of this investigation was to analyse the most current findings about NSCLC metastasis. In regard to discussing the challenges of LC identification and treatment, this research dives into the issue of LC model systems, along with metastasis, pathways across SCLC transmission, and LC-specific challenges. The goal of this analysis is to serve as a benchmark for future studies in this area while also offering helpful clinical pointers for patients.

**Robles-Oteiza et al.** [58] stated that the speedy distribution of vaccines in response to the COVID-19 pandemic provided researchers in the field of cancer vaccine research with valuable insights that have contributed to the field's current renaissance. Recent clinical trials have also shown that cancer vaccines are not only safe and feasible, but that they can also be associated with the creation of antigen-specific memory T cells and, in some cases, durable clinical responses. These findings demonstrate that cancer vaccines are not only safe and feasible, but that they can also be affiliated with the generation of antigen-specific memory T cells. These results were obtained by utilizing various delivery platforms, such as mRNA and synthetic long peptides, amongst other things. In spite of these advancements, fundamental questions concerning the most efficient delivery platforms and antigen targets that could be used in cancer vaccines still need to be answered. These questions could be answered by conducting further research. It is hoped that studies currently being conducted as well as those that will be conducted in the future that make use of recent advancements in the identification of new sources of antigens, the prediction of immunogenic antigens, as well as the usage of single-cell technologies to profile antigen-specific T cells would then reveal correlations to clinical outcomes and provide a mechanistic foundation for future progress.

## 2.2. RISK FACTORS OF LUNG CANCER

This disease has seen a significant rise in prevalence as a result of shifts in dietary practices and lifestyle choices, as well as the introduction of various types of food additives, synthetic

chemicals, environmental pollutants, various forms of radiation, and restricted opportunities for physical activity.

**Xue, Y., et al** [59] researched particularly the environment of fast socioeconomic growth and the spread of urbanisation, air quality is a worldwide healthcare concern. The author explains how both outdoor and interior contaminants may be dangerous to one's health, particularly the lungs. Fine particles in the air, such as those emitted by factories and cars, have been linked to lung cancer (LC). Asbestos, PAHs, and toxic metals all increase the risk of LC for workers. In the home, LC may be spread via gases from cooking, indirect smoking of home. Microbes like viruses and bacteria are also major contributors to healthcare problems including "lung inflammation" and cancer. "Inflammation", "DNA damage", and "epigenetic regulation" are all described in depth as examples of the specific impacts of LC brought on by air quality. In furthermore, the latest innovations in environmental protective technologies and government initiatives to curb air quality are outlined. Author's overview serves as a springboard for more studies on the link between LC and air quality.

Smoking is the leading risk factor for lung cancer [60]. When cigarettes became the major tobacco product manufactured in the 1900s, lung cancer became more common. Increases in the number of years or the number of packs smoked per day increases the degree of risk for lung cancer [61]. Smoking causes at least 80% of lung cancer deaths. A relative risk of developing lung cancer from passive smoking was found to be 1.14 to 5.20 in people who had never smoked but lived with a smoker based on a metaanalysis and comprehensive review [62]. People living with a smoker can increase a nonsmoker's chance of developing lung cancer by about 20–30% [63].

Lung cancer is considered one of the most common cancers caused by occupational exposures. Radon, a naturally occurring carcinogen, is among the risk factors linked with lung cancer, and approximately 21,000 lung cancer deaths in the United States have been linked to radon exposure [64]. Although radon was initially linked with mine workers, there has been increasing concern attributed to indoor radon exposure from natural uranium deposits that are commonly found in basements. A collection of case-controlled studies from North American, Europe, and China has demonstrated increased incidence rates of lung cancer linked to residential radon exposure at levels of 2.7 picocuries per liter (pCi/L). The use of asbestos in industry or

manufacturing has been linked to increased incidence of mesothelioma and lung cancer. An association between asbestos fiber sizes as a strong predictor of lung cancer mortality has been found [65-70].

Other occupational exposures linked to lung cancer include the use of arsenic and arsenic compounds (antifungal, outdoor wood preservatives, insecticides, herbicides, etc.), exposure to beryllium and beryllium oxide (X-ray and radiation technology, etc.), inhaled chemicals including cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl esters and diesel exhaust. In big cities and other areas with traffic congestion, longterm and accumulated exposure to air pollution, including emissions composed of polycyclic aromatic hydrocarbons, is identified as a lung cancer risk factor. Air pollution has been associated with an 8% increased risk of all-cause lung cancer mortality. Personal or family history of lung cancer serves as a risk factor for a person to develop lung cancer [71-75].

There are certain genes and chromosomes that have been linked to an increased risk of lung cancer. Carriers of TP53 germline sequence variations who also smoke are more than 3 times more likely to develop lung cancer than nonsmokers. There are also reports of a marker on chromosome 15 associated with lung cancer, which was explored in three independent genetic studies [76-79]. The marker contains three genes for subunits of the nicotine acetylcholine receptor. Cell change can occur when nicotine latches on to this protein, located on the cell surface. Based on results from these three independent studies, people with one copy of the marker have a 30% increased risk of developing lung cancer, while people with two copies have an increased risk of 70–80%.

**Siwik et al.** [80] hypothesised that since smoking is linked to LC, LC patients would be greater prone to experience regret and humiliation, increasing their likelihood for stress. Author used hierarchical multiple regression to examine the possibility that guilt is more strongly linked to depression than shame. Three different regression models were used to examine the links between self-compassion and negative emotions such shame, guilt, and depression. When attempting to explain depressed signs, the most effective model included shame but not guilt. Lowered levels of shame and depressive symptoms were linked to increased self-compassion, but guilt was not. These results provide support for interventions that help people with LC who

have a history of smoking overcome feelings of guilt by strengthening their capacity for self-compassion.

**Peravali et al.** [81] has hypothesized that people who have LC cancer is an independent predictor for serious infection and greater mortality in people who have coronavirus disease (COVID-19). The author aims to summarize patient characteristics, obstacles in diagnosis and therapy, and treatment outcomes for individuals with COVID-19 who have LC. A meta-analysis was carried out for the COVID-19 linked mortality that is connected with LC in comparison with other types of cancer. The results were reported using the odds ratio (OR) as well as confidence intervals. The mixed-effects logistic regression model was used. Fever and cough were the most commonly reported clinical findings in patients with LC who were treated with COVID-19. These two symptoms were experienced by 68 and 61 percent of patients, respectively. The results of the laboratory and radiographic examinations were in line with the generally published data. According to the findings of the meta-analysis, the mortality rate was significantly higher in patients who had LC compared to the mortality rate in patients who had other types of cancer, with an OR of 1.62 (95 percent confidence interval: 1.06–2.48) Patients diagnosed with LC who carried the COVID-19 gene also displayed a more severe disease, as well as higher admission rates to critical care units and higher rates of breathing by mechanical means. In patients with LC, the presence of COVID-19 is related with more severe disease and a higher risk of death in comparison to patients with other types of cancer and the general population. The evidence regarding the influence that certain LC treatments have on outcomes is mixed and inconsistent. Treatment aimed at LC should be continued or restarted as early as feasible in mild to moderate instances in order to avoid the disease from getting worse and death from cancer-related causes.

## 2.3. MODERN TREATMENT OF LUNG CANCER

Patients who have stage I, II, and IIIA NSCLC typically have surgery to remove the tumor if the tumor is found to be resectable and the patient is able to tolerate surgery. Surgeons may remove a lobe or section of the lung containing the tumor. To determine if the tumor is resectable, imaging studies and biopsies are completed as well as an evaluation of patient factors to determine operability. Currently, many surgeons utilize video-assisted thorascopic surgery (VATS), where a small incision is made in the chest and a thorascope is inserted. A lobe can be removed via the scope through this small incision so that a larger incision does not have to be made [82].

Some patients who have undergone a resection surgery may benefit from adjuvant therapy in reducing the risk of lung cancer relapse. Adjuvant therapy may include radiation, chemotherapy, and targeted therapy. Patients with stage IIA, IIB, and IIIA NSCLC usually receive chemotherapy after surgery to kill any remaining cancer cells in order to prolong survival [83].

Approximately 40% of newly diagnosed lung cancer patients are stage IV. The goal for treating these patients is to improve survival and reduce disease-related adverse events. For stage IV NSCLC, cytotoxic combination chemotherapy is the first-line therapy, which might be influenced by histology, age vs. comorbidity, and performance status (PS). The American Society of Clinical Oncology states that treatment for a patient with a PS of 0 or 1 is a regimen of a platinum (cisplatin or carboplatin) plus paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, or pemetrexed [84, 85]. Results from four large multicenter randomized clinical trials studying the above agents with either platinum or carboplatin have yielded similar results. From these studies, results have shown that no single regimen demonstrated a significant superiority over any other combination. Median overall survival for patients in these studies was approximately 8–10 months. The specific combination depends on types and frequencies of toxic effects and should be decided on an individual basis. However, adenocarcinoma patients may benefit from pemetrexed. Cisplatin is the slightly more effective platinum, however it has been associated with more side effects. For patients with a PS of 2, evidence suggests that they may need only one drug, which is typically not platinum [86-90]. For chemotherapy treatment, serious adverse events should prompt a change in agents. Therapy should also be stopped if the cancer grows or if, after four treatment cycles, the disease is stable but the treatment is not shrinking the tumors [90-91]. Patients with a PS of 3 do not typically benefit from receiving cytotoxic chemotherapy because the risk of adverse events could worsen their quality of life significantly. For these patients basic supportive care is generally recommended.

Radiotherapy uses high-energy beams to damage DNA within cancer cells, thereby destroying them. This therapy can help control or eliminate tumors at specific sites in the body. Patients with NSCLC that is localized to the chest and who are not candidates for surgical resection may benefit from radiotherapy. Radiotherapy also can be part of palliative care to improve quality of life in NSCLC patients who do not respond to surgery or chemotherapy [92]. A technique called stereotactic body radiation therapy (SBRT) is used for early-stage NSCLC patients who have a

single small nodule in the lung without any metastases to nearby lymph nodes. This technique uses an advanced coordinate system to precisely locate the tumor and ensure precise placement of the tracking device. This enables delivery of concentrated and highly focused radiation treatment. In a meta-analysis comparing the effectiveness of radiotherapy with photons, protons, and carbon-ions for NSCLC, it was found that SBRT offered greater 2-year overall survival rates, lower costs, and greater patient convenience [93]. In a prospective phase II study, 50-month results of 70 medically inoperable patients receiving SBRT showed that receiving SBRT resulted in high rates of local control in medically inoperable patients with Stage 1 NSCLC. In a phase III multicenter study of patients with early stage but medically inoperable NSCLC, toxicity and efficacy of SBRT was studied. Of the 55 patients evaluated, it was found that patients who received SBRT had a survival rate of 55.8% at three years along with moderate treatment-related morbidity [94-96].

**Jasper et al.** [97] conducted community ablative treatments, such as surgeries or "stereotactic radiotherapy" (SABR), are emerging a progressively essential element in the cure of "oligometastatic" illness in NSCLC, as has been examined, NSCLC is a possible cause of this condition. In this review, author compile the most up-to-date randomised data showing that such individuals can gain advantage from local embolization in terms of both progression survival and overall survival. This proof comes from research done during the last several years. Furthermore, author talk about the upcoming results from phase III, which should help us understand the ideal therapy parameters and learn more about the "oligometastatic" state. As "oligometastatic" disease is a portion of non-small-cell LC, we first go through a contemporary foundation for distinguishing patient, tumour, and therapy personality qualities that may best steer care. There is a relatively minimal chance of this illness extending to other parts of the body. Since it might be difficult to provide effective leadership while dealing with "oligometastatic" illness, this is crucial.

**Yin, X., et al.** [98] conducted the type of neuroendocrine tumor known as SCLC that has been studied has a high rate of malignancy and a poor prognosis. There is a subtype of SCLC known as transformed SCLC, which is very similar to de novo SCLC in terms of its pathological morphology, molecular characteristics, clinical manifestations, and sensitivity to drugs. However, the pathogenesis and the microenvironment of the tumor are different in de novo

SCLC compared to transformed SCLC. NSCLC patients who have developed resistance to chemotherapy, immunotherapy, or targeted therapy may have done so as a result of their SCLC transformation. The pathogenesis of SCLC transformation has been attempted to be explained using two different hypotheses. Even though SCLC transformation is not very common in clinical practice, it has been identified time and time again in a variety of patient series and case reports involving small patient populations. After treatment with tyrosine kinase inhibitors, it most frequently occurs in epidermal growth factor receptor (EGFR) mutant lung adenocarcinoma (TKIs). SCLC transformation can also occur in patients whose LC tests positive for anaplastic lymphoma kinase (ALK) after treatment with ALK inhibitors, as well as in patients NSCLC with wild-type EGFR or ALK that is treated with immunotherapy. Chemotherapy was once a common treatment for patients who's SCLC had become transformed; however, the prognosis following chemotherapy is poor. We aim to provide a better understanding of transformed SCLC and provide support for clinical uses by conducting a comprehensive review of the improvements in changed SCLC. This review covers clinical and pathological characteristics of transformed SCLC, as well as potential effective treatments for SCLC patients who have undergone transformation.

**To, C., et al.** [99] Patients with EGFR-mutant LC originally respond well to treatment with small-molecule "Tyrosine Kinase Inhibitors" (TKIs), but ultimately acquire sensitivity to these drugs, according to a study. To counteract the effects of EGFR alterations that render patients resistant to standard ATP-competitive EGFR TKIs, researchers have created allosteric EGFR inhibitors that target a different location on the EGFR. This is due to EGFR does not have to interact with ATP for binding with allosteric EGFR inhibitors. This research recognises and characterises JBJ-09-063, a chimaera allosteric EGFR inhibitor that inhibits EGFR in both resistant and sensitive designs, including those with "EGFR T790M and C797S mutations". Keep in mind that JBJ-09-063 works for a broad variety of EGFR mutations. Furthermore, we discover that the EGFR L747S mutation, in addition to "homodimerization" or "heterodimerization" with other ERBB families, confer resistance to JBJ-09-063, but not to ATP-competing EGFR TKIs. Collectively, our findings demonstrate the potential therapeutic benefit of JBJ-09-063, either as a monotherapy or in conjunction with EGFR TKIs, to identify more efficacious methods for treating LC caused by EGFR mutations.

**Pham, J., et al.** [100] studied the treatment “tolerability”, “toxicity”, and inadequatemedical trial statistics in the mature significantly impede the treatment of elderly patients diagnosed with LC. This may give increase to cure“nihilism amongst clinicians”. The purpose of this study is to investigate potential factors that contribute to excessive mortality and to describe the survival rate of patients over the age of 65 who have LC. (n = 3481) of the patients who were treated with LC in the “Victorian” LC between the years 2011 and 2018 were taken into consideration for this study. After taking into account any potential confounding factors, patients were classified according to their ages before being compared using a method called cox regression modeling. In addition, the likelihood of being offered cancer treatments was calculated and then stratified according to the progression of the disease. Patients who were older than 80 years old had a median survival time that was significantly lower than that of patients in younger age groups (median survival times for patients under 60 years old were 2.0 years, for patients 60–69 years old it was 1.5 years, for patients 70–79 years old it was 1.6 years, and for patients over 80 years old it was 1.0 years; p 0.001). Adjusted death rates did not vary significantly between younger and older patients with a stage 1 or stage 2 diagnosis of LC at any time throughout the trial. Individuals older than 60 years old had a 28% higher modified mortality probability than participants younger than 60 years old (p=0.005) if they were identified with stage 3 or 4 illness. Even after adjusting for characteristics including sex, functional condition, comorbidity, and histological type, the likelihood of receiving cancer therapy was considerably lower among those in this age group. Although if performing level and comorbidity are comparable to those of younger patients, older individuals with advanced-stage LC have a proportionally greater risk of death and a reduced chance of obtaining cancer therapy. This is true even when contrasting elderly and younger individuals suffering from the same illness. These inequalities in health care may be symptomatic of a more ubiquitous and deleterious perspective on the healthcare of the aged.

## 2.4. MEDICINAL PLANTS FOR TREATING CANCER

Cancer is a disease that can be found in all parts of the world's human population. There is a constant desire for innovative drugs that can treat and prevent this life-threatening illness. The belief that natural-derived drugs, such as chemotherapy, have less potentially adverse side effects than traditional medicines like radiation and chemotherapy is garnering the attention of scientific

and academic communities. Natural secondary metabolites that are generated by plants are now being investigated for their potential anticancer effects, which might result in the development of innovative new medicinal drugs. As a direct consequence of these compounds' level of efficacy, which has led to their adoption as industry standards for the treatment of cancer, new technologies are being developed to propel the area even farther. Nanoparticles for nanomedicines, for instance, are an instance of a recently developed technology that intends to improve the anticancer capabilities of plant-derived pharmaceuticals by controlling the release of the component and researching new methods of distribution. The importance of naturally occurring compounds derived from medicinal plants and the characteristics of those plants that produce them potential anticancer treatment targets are both highlighted in this research article [101].

Cancer chemoprevention, as characterized by scientific research, is the practise of using artificial, organic, or biologic substances to reduce the risk of tumor in otherwise healthier people. Chemicals used for cancer prevention work either by arresting or inhibiting the development of pre - malignant cells containing DNA mutation, both of which are necessary steps on the road to malignancy. Clinical studies including patients with lung, prostate, and colon cancer have shown the method's efficacy. The rising number of cases of cancer, the ineffectiveness of standard chemo, and the unacceptable side effects of chemo all point to the need for a new strategy non the fight against cancer. "Chemoprevention" with "tamoxifen" was initially tested on LC patients, and the results showed a substantial reduction in invasive LC. The rationality and potential of utilising chemoprotective drugs to protect high-risk people from cancer has been shown. “Capsaicin", "cucurbitacin B", "isoflavones", "catechins", "lycopene's", "benzyl isothiocyanate", "phenethyl isothiocyanate", and "piperlongumine" are only few of the dietary elements that have shown inhibitory activity on cancerous cells, suggesting they may function as chemoprevention. Numerous natural compounds have been shown to have cancer-preventing and -killing properties have reviewed their underlying mechanisms [102].

The cancer of the leukocytes is known as leukemia, and it is distinguished from other types of leukocyte cancer by the uncontrolled proliferation of immature immune cells in the bone marrow, blood, and spleen. There are many different types of leukemia, and the type of leukemic disease a patient has will determine both the most effective treatment plan and the patient's

chance of survival. The disease known as leukemia has been treated with a variety of drugs in the past. The search for safer and more effective drugs continues to be one of the most difficult areas of research due to the negative effects that are associated with such therapies and the development of drug resistance. Therefore, novel therapeutic approaches are essential to making progress in patient care. Almost half of the pharmaceuticals that are used today in the treatment of cancer are derived from natural products or natural products' derivatives. It has been demonstrated that medicinal plants are an efficient natural source of drugs that can treat leukemia. The cytotoxicity of these plants, as well as the mechanisms that lie behind the toxicity of these plants to leukemic cells and their isolated compounds, was looked into. Throughout the entirety of this extensive review, efforts have been made to highlight recent developments and milestones achieved in leukemia therapy utilizing plant-derived compounds and the crude extracts from a variety of medicinal plants. In addition to that, the ways in which these plants exert their effects are discussed [103].

The prevalence of cancer and the fact that it is one of the most significant causes of morbidity and mortality in the world, the discovery of novel anticancer drugs is of utmost importance. The previous century was marked by significant developments in the fields of plant and microbiology research, which led to the discovery of a number of compounds that are now utilized in the treatment protocols for cancer. Natural products, such as plants, marine organisms, and microorganisms, are the source of a significant number of successful anticancer drugs that are currently used in clinical settings and have demonstrated significant efficacy. As a result of recent developments in proteomics and metabolomics, there has been a surge in the identification of new therapeutic targets, which has led to the development of new therapeutic perspectives. More than half of all the molecules that were given the green light between 1981 and 2014 came from natural products or were derived from them, and the vast majority of these molecules were anticancer agents. Within this framework, natural products have been recognized as abundant and fruitful sources for the development of new cancer treatments. The author highlights both the anticarcinogenic potential of natural products as well as the importance of the discovery of new plant-derived metabolites for use in cancer therapeutics. The author focuses on the importance of the discovery of new plant-derived metabolites. The author also talks about the most significant natural-derived drugs that have recently been introduced to the pharmaceutical market [104].

There are several synthetic anticancer drugs that are currently on the market, but their clinical utility is severely limited due to the adverse effects and interactions they cause with other medications. It is common knowledge that the majority of the chemotherapy drugs that are currently being used to treat cancers can cause the disease to become resistant to treatment, display non-selective toxicity toward normal cells, and have dose-limiting side effects. As a result, the treatment of cancer and the creation of drugs for this disease continue to be a significant clinical challenge. On the other hand, plants are an exceptionally viable source of biologically active natural products. These naturally occurring tumor treatments have the potential to be used as standalone businesses or as the starting point for the creation of altered compounds with enhanced efficacy and decreased toxicity. There is growing interest in herbal remedies as potential reservoirs of antitumor drugs. In addition to being extensively employed because their raw ingredients are easily accessible, they are inexpensive, have few if any negative side effects, may be utilised in a variety of contexts, and are effective as therapies. As a consequence of its efficacy and lack of side effects, traditional medicines are advocated for by the "World Health Organization" (WHO) [105].

This disease has seen a significant rise in prevalence as a result of shifts in dietary practices and lifestyle choices, as well as the introduction of various types of food additives, synthetic chemicals, environmental pollutants, various forms of radiation, and restricted opportunities for physical activity. Foods high in beneficial nutrients and plant chemicals called phytochemicals play an important part in boosting the body's immune system, which is an important step in warding off various cancers. Phytochemicals are natural bioactive compounds that do not contain any nutrients and are derived from a wide variety of plant sources. They lower the risk of developing serious chronic diseases. On the basis of its chemical make-up and the mechanism by which it exerts its biological influence, it is straightforwardly divisible into a number of distinct groups. These biologically active compounds have been shown to be effective against a wide variety of cancers. Recently, the potential role of a number of novel phytochemicals and nano formulations has been investigated, and these therapeutic approaches have seen extensive application. The management of cancer can make use of a wide variety of traditional phytochemicals as well as novel nano formulations, which were discussed by Binothman, N. [106].

**Hashem, S., et al.** [107] demonstrated that the cancer ranks among the top causes of death and places a significant burden on the nation's healthcare system. There is without a doubt an unmet need for the discovery of new anticancer drugs due to the prevalence of the disease. Because of their availability, applicability, and reduced cytotoxicity, the use of natural products as anticancer agents is a therapeutic approach that is considered acceptable. In the contemporary period of drug research and development, natural products have provided an unparalleled source of potential anticancer medications. Natural products, along with their derivatives and analogs, play a significant part in the treatment of cancer. They do this by modulating the microenvironment of the cancer and various signaling pathways. These compounds are effective against a number of different signaling pathways, most notably those associated with the death of cells (apoptosis and autophagy) and those associated with embryonic development (Notch pathway, Want pathway, and Hedgehog pathway). Natural products have a solid track record throughout history; however, there is a pressing need to investigate the current role that natural products play in the discovery and development of cancer drugs. Additionally, it is necessary to determine whether or not natural products have the potential to become an important source of future therapeutic agents. Due to the fact that many target-specific anticancer drugs have failed to provide successful results, there is a necessity to investigate natural products that possess multi-target characteristics in order to achieve better results. Because natural products have the potential to contain novel compounds that show promise in the treatment of cancer, studying them has become an important area of research. The purpose of the authors review is to investigate the significance of natural products in inhibiting the various signaling pathways that serve as drivers of carcinogenesis and, as a result, pave the way for the development and discovery of anticancer drugs.

**Nerkar, A. G.,** [108] stated that the natural products have been extremely important in the diagnosis and treatment of a wide variety of human diseases. The discovery of penicillin fundamentally altered the course that modern medicine would take. In light of the fact that quinine was traditionally used to treat malaria, willow bark was traditionally used to treat pain, and a number of other natural products were used as medicines in ancient medical systems such as Ayurveda and traditional Chinese medicine, the discovery of medicines for allopathic use that come from natural sources has garnered a significant amount of attention. The ancient medical practice known as Ayurveda includes a section that discusses the use of various plant extracts in

the treatment of cancer. The use of a diet similar to that of the Mediterranean and the inclusion of fruits and vegetables have both been described as scoring low as risk factors for various cancers based on prevalent epidemiological factors. Additionally, a number of discoveries have resulted in the modification of the dynamic components of naturally occurring products derived from dietary sources for the purpose of chemoprevention. Significant clinical tests conducted in the process of developing drugs derived from marine and microbial origin have been fruitful and positive in terms of developing drugs that are both safe and effective. On the other hand, the success rate is extremely low because natural products are not readily available in the large gram quantities that are necessary for clinical trials. The total synthesis of multiple naturally occurring products derived from marine origin has also emerged as a solution to this problem. This has resulted in the successful development of four marine drugs as anti-cancer agents. Moreover, this issue has been successfully resolved. The author provides an overview of the anticancer drugs that originate from natural sources and are used as chemo preventive and chemotherapeutic agents. In as many places as possible, the specifics of the clinical trials, as well as their applications and mechanisms of action, have been covered.

**Rajasekar, N.,** [109] suggested that the development of medication resistance in tumor microenvironment and the spread of disease to distant organs make conventional anti-cancer medications useless, despite the availability of a wide variety of novel methods to cancer therapy. A lot of people these days are curious in herbal medicines as a substitute to conventional medicine. It's because these medications have less negative consequences and have a significant absorption. A class of polyphenolic compounds known as tannins is present as a byproduct in many different kinds of produce and nuts. "Anti-inflammatory", "anti-fibrotic", "anti-microbial", "anti-diabetic", and other therapeutic characteristics of tannins have been discovered. This study aims to do just that by providing a condensed assessment of what is currently known about the molecular processes behind the anti-cancer benefits of dietary tannins. Numerous oncogenic components, including transcription factors, growth factors, receptor kinases, and many more, have been shown to be inhibited by tannins in in vivo and in vitro studies, providing evidence that tannins have anti-cancer actions. The ADMET qualities of tannins, the outcomes of clinical studies, and author’s recommendations for the future of tannin research were also discussed.

**Al-Yozbaki, M., et al.** [110] studied that natural medicines offer promise and potential efficacy in the treatments of LC, and they have minimal unfavourable side effects. The synergistic activity of an anti-cancer medicine and a natural molecule may improve the therapeutic effect against cancer cells, but the anti-cancer treatment alone cannot do this. Apoptosis is abnormally regulated in cancer, which aids the survival of cancer cells and so advances the illness. Alterations in genes that control cancer are caused by many cancer treatments; these alterations should kill cancer cells, but rather they make cancer cells resistant to chemotherapy. To induce a cytotoxic impact on the cancer cell, several treatments rely on naturally occurring chemicals that may specifically target certain cell signalling pathways. Recent advances in medicine have resulted in the creation of several medicines with dual effects, and it is getting clearer by the day just how important these substances are. The author focuses on the cell signalling pathways involved in the action of a number of these organically available chemicals on LC cells. More study is needed to determine the efficacy of natural chemicals in treating of cancer.

**Vijayakurup, V., et al.** [111] proposed that despite a general decrease in smoking and tobacco use, an alarmingly higher number of people are being diagnosed with LC each year. Recent research suggests that there is a very strong connection between the rise in popularity of fast food and the incidence of LC. Benzo[a]pyrene, also known as B[a]P, is a powerful carcinogen that is found in high concentrations not only in smoked tobacco products but also in foods that have been grilled or deep-fried. Curcumin has been shown to be effective in preventing B[a]P-induced lung carcinogenesis in the studies that authors have conducted in the past. On the other hand, the compound has a poor pharmacokinetic profile, which significantly hinders its potential as an effective chemo preventive agent. The purpose of the study was to determine whether or not encapsulating curcumin in chitosan nanoparticles can enhance cellular uptake, increase the amount of time curcumin is retained in tissue, and ultimately result in improved chemoprevention. Using transmission electron microscopy, the size of the curcumin-loaded chitosan nanoparticles, also known as chitosan nanocurcumin, was measured to be between 170 and 200 nm. In vitro drug release studies demonstrated that curcumin had a sustained release over a period of approximately 180 hours. These studies also demonstrated that LC cells had excellent intracellular uptake and cytotoxicity. When compared with free curcumin, bioavailability studies conducted with healthy Swiss albino mice demonstrated a significant increase in the amount of chitosan nanocurcumin that was localized in the lungs. The

formulation was shown to be pharmacologically safe after undergoing toxicological testing using a model of chronic toxicity that was performed on Swiss albino mice. Furthermore, the formulation, even at a dose equivalent to one fourth that of free curcumin, exhibits better efficacy in reducing tumor incidence and multiplicity than free curcumin, thereby hindering the development of B[a]P-induced lung adenocarcinomas in Swiss albino mice. This was determined by testing the formulation on mice with lung adenocarcinomas caused by B[a]P. Because of this, the findings demonstrate that the formulation is superior to free curcumin and establish it as a candidate for use as a chemo preventive agent as well as an oral supplement against environmental carcinogenesis.

**Kasala, E. R., et al.** [112] also studied the B (a) P induced LC in mice provides a relevant model to study the effect of natural products. This model has been widely used by a large number of researchers, and they have found considerable success in ameliorating the pathophysiological changes associated with LC. In and of themselves, the synthetic drugs that are currently on the market and which make up the pharmacological arsenal are effective in treating the condition; however, they are not without their drawbacks. These hypotheses have sped up the demand for natural products, which can be taken as a dietary supplement to slow or stop the progression of LC. In addition to that, the use of these agents in conjunction with the standard treatment not only improves the overall management of the condition but also results in fewer negative side effects. In the present review, we are attempting to give a silhouette of the mechanisms of B (a) P induced lung carcinogenesis and the role of dietary phytochemicals in chemoprevention. This is in the context of the rising interest in dietary phytochemicals as newer pharmacological interventions for LC.

## 2.5. ANTICANCER MEDICINAL PLANTS OF INDIAN ORIGIN

Several pharmaceutical industries derive a significant amount of the synthetic and herbal agents they use from plant sources. Several of the most important plant-derived compounds, including vinblastine, vincristine, topotecan, and paclitaxel, all played a significant part in the research that led to the development of anticancer drugs that have proven effective in clinical trials (taxol). Himalayan plants are a rich source of a variety of secondary metabolites including anthraquinones, flavonoids, tannins, alkaloids, and many others. These plants grow at high altitudes in the Himalayas. This review article discusses the active constituents that were isolated

from a variety of cancer-fighting plants found in the Himalayas, as well as their effect on a variety of cancer-fighting cell lines. It has been demonstrated throughout history that plants of Indian origin and the metabolites that they produce have significant therapeutic potential in the treatment of a wide range of acute and chronic diseases. Because of their high activity and low toxicity, the novel bioactive compounds that can be extracted from a wide variety of plants are currently the subject of research as potential therapeutic agents. The author provides a detailed account of various medicinal plants that have been researched for their possible ability to fight cancer [113, 114].

**Ali, R., et al.** [115] examined the potential for naringenin to act as a protective agent against the oxidative stress and pulmonary toxicity induced by benzo[a]pyrene (B[a]P). Oral gavage administration of naringenin at a dose of 100 mg/kg body weight (b. wt.) was used to administer treatment to the rats. Intraperitoneal administration of B[a]P at a single dose of 50 mg/kg body weight was performed. For the purpose of determining whether or not naringenin exerts a protective effect, measurements were taken of the following: total protein, total cell counts, lactate dehydrogenase, lipid peroxidation, reduced glutathione, antioxidant enzymes activities; lung histology; and the expression of nuclear factor kappa B (NF-kB) and cyclo-oxygenase-2 (COX-2). In addition, histopathological and immunohistochemical examinations were carried out to investigate the toxicity and inflammation of the lungs. The administration of B[a]P resulted in an increase in the levels of lung injury markers and a reduction in the activities of antioxidant enzymes. The treatment with naringenin reduced the levels of oxidative stress by restoring antioxidant enzymes. This resulted in further improvement of lung histological damage and a significant reduction in inflammatory responses. Additionally, the expression of NF-B and COX-2 that was induced by B[a]P was effectively decreased by naringenin. These findings suggest that supplementation with naringenin is beneficial in maintaining the integrity of alveoli and the epithelium. This compound has the potential to be used as a protective agent in B[a]P-induced oxidative stress and lung damage. However, additional research is required in order to shed light on the possible mechanism of action that naringenin possesses.

**Shakya, A. K.** [116] mentioned that the ayurveda, which is the traditional medical approach that makes use of herbs, has a long history and a solid foundation in India. Plants used for medicinal purposes are of great value in both the prevention and treatment of illnesses affecting humans.

Since the beginning of recorded history, people have used various plants to make traditional medicines. In every region of the world, the rise of human civilization has been linked to the domestication of various plant species. Plants, on the other hand, are thought to be rich sources of phytochemical ingredients, which are the components that enable them to have medicinal value. Plants with medicinal properties have the potential to be mined for the production of novel herbal medicines. In the 21st century, the pharmacological effects of medicinal plants have been taken into consideration as a potential future drug or medicine for the administration of health care. In recent years, there has been resurgence in interest to rediscover medicinal plants as a source of potential drug candidates. This interest comes from the rediscovery of medicinal plants dating back centuries.

**Hamid, I. W., et al.** [117] investigated the effects of an extract made from the leaves of the *Centella asiatica* plant on a mouse model of LC caused by benzo(a)pyrene. In this study, 30 newborn baby mice were used, each of which was separated into one of six groups. The positive control, also known as group I, was given benzo(a)pyrene at concentrations of 0.2 mol on day one, 0.4 mol on day seven, and 0.8 mol on day fifteen, but no extracts were used. Tamoxifen was used as the treatment for Group II, and benzo(a)pirene was used as the inducer. On day 25, groups III, IV, and V were given 250, 500, and 750 mg/kg bw of extract from *Centella asiatica* leaves respectively. Group III served as the negative control and received only the DMSO solvent. A statistically significant difference (p 0.05) was found between the amount of benzo(a)pyrene that was induced by lung tumor nodules and the extract of *Centella asiatica* leaves. The treatment with doses of extract ranging from 250 to 750 mg/kg bb did not result in a statistically significant difference ($p > 0.05$) in the mean number of lung tumor nodules. An analysis of the lung's histopathological features using a microscope revealed a reduction in the number of tumor foci in the bronchus and alveolar septum, as well as an inhibition of bronchial epithelial cell hyperplasia. The development of benzo(a)pyrene can be prevented and the number of tumor nodules can be reduced using an ethanolic extract of the *Centella asiatica* plant. The component of the seeds of *Borreria hispida* and *Momordica dioica* for their effects on cancer cell proliferation also extensively studied [118].

## 2.6. ANTICANCER MEDICINAL PLANTS OF FOREIGN ORIGIN

**Madhuri and Pandey** [119] studies medicinal herbs of overseas heritage had proven useful in people and testing animals with different forms of malignant and benign tumours. *Agrimonia pilosa* for sarcoma, *Ailanthus altissima* for intestinal cancer, sarcoma, and leukaemia. To find *Fritillaria thunbergia* in pulmonary, lung, throat, and stomach malignancies; The use of *Larrea tridentata* in the therapy of many types of cancer, including leukaemia; Ascites tumours and sarcomas treated with *Lonicera japonica*; *Nidus vespa* in stomach and liver tumours; Lymphoma, sarcoma. Potential has been found for the use of *Pyrus malus* in the treatment of malignancies of the lung, colon, and intestines; Evidence suggests that *Scutellaria barbata* may be used to effectively treat sarcoma and Ehrlich's ascites carcinoma.

A large number of natural products isolated and identified from Chinese medicinal herbs have been investigated for their anticancer potential. For example, the famous chemotherapeutic drugs including cisplatin and taxanes, were discovered via cytotoxic phenotype investigation and followed by the identification of their mechanisms of molecular actions. Some others were developed from target-based discovery, such as epothilone (target tubulin) and temozolomide (target DNA). Magnolol, a component isolated from *Magnoliae Officinalis Cortex*, was reported to possess anticancer effects against human breast cancer via inhibiting EGFR signaling pathways. Recently, researchers have found that curcumin, isolated from *Curcumae Longae Rhizoma*, decreased PD-L1 expression and then sensitize the cancer cells to anti-CTLA4 therapy [120].

**Wu, X., et al.** [121] studied traditional Chinese medicine and other plant extracts in the treatment of illnesses, particularly malignant tumours. Many of the active substances in herbal treatments, however, have either not been identified or have been discovered but not adequately developed and utilised. Because of this, the screening of novel active components in Chinese medicine and the determination of their anticancer effects has become a major advancement in the treatment and prevention of tumour illness. Numerous studies, including our own anticancer research on resveratrol in colorectal cancer, have shown that *Polygonum cuspidatum* and its active components like resveratrol exhibit good antitumor properties. This article aims to give a theoretical foundation for future scientific studies and clinical applications by summarising the

research advances made on the Chinese herb *Polygonum cuspidatum* and its active components in the treatment of malignant illnesses.

Formulae are the main forms of Chinese medicines used in clinic, which also play an essential role in cancer therapy. Numerous formulae have been recorded, but the working mechanisms for most of them remain unknown. Clinically, they are often used in combination with conventional drugs to achieve a synergistic anticancer effect or to reduce the side effects. For example, the formula *Xue-Fu-Zhu-Yu-Tang* decreased the tumor weight by enhancing the immune function in the tumor-bearing mice, and the combinational use of *Xue-Fu-Zhu-Yu-Tang* increased the effect of chemotherapy. The *Sheng-Mai-Yin* can relieve the myocardial toxicity caused by doxorubicin. However, the difficulties of quality control and mechanism study still represent the main obstacles for the development and clinical usage of Chinese medicinal formulae [120].

## 2.7. PHYTOCHEMICALS: TREATMENT OF LUNG CANCER

The use of medicinal plants dates back to the beginning of civilization, as is most clearly demonstrated by the existence of ancient script and the recipe for traditional herbal medicine. In spite of the historically rich demonstration about the use of plants as therapeutics, the drug companies lack interest in the research of phytochemicals in comparison to the research of synthetic drugs. For the most part, the lack of information about tree medicinal therapeutics is responsible for attracting the attention from researchers to believe about organic ingredients as potential drugs for detrimental diseases such as cancer. In order to bridge the information gap between plant biology and clinical researchers, this review will cover clinically successful tree anticancer drugs as well as underappreciated drugs that have the potential to treat cancer. In addition, unprecedented advancements in synthetic chemistry, omics studies to pin point the target gene function, and efficient drug delivery systems have made it much easier for research to explore a phytochemical as an effective anticancer drug. These factors have all contributed to the success of this endeavor [122].

It is believed that phytochemicals found in plant-based diets contribute significantly to the prevention of LC and that these phytochemicals may be effective at targeting LC stem cells. The author compiled recent research on lung homeostasis, carcinogenesis, and phytochemicals that have been studied in relation to LCs. We provide an in-depth analysis of how normal lung tissue functions and relate this to the process of lung carcinogenesis in order to redefine better targets

for LC stem cells. Curcumin, resveratrol, quercetin, epigallocatechin-3-gallate, luteolin, sulforaphane, berberine, genistein, and capsaicin are the nine well-studied phytochemical compounds that are discussed in this article in terms of their chemo preventive and anticancer mechanisms in LC as well as their potential use in the clinic. The author also focuses on the ways in which the use of phytochemicals can be improved through structural manipulations, targeted delivery, adjustments to concentration, and combinatorial treatments. Our contention is that lung carcinomas ought to be handled differently according to the distinct cellular origins of each individual tumor. It seems like targeting pathways that induce quiescence, reduce inflammation, or maintain a healthy balance of reactive oxygen species would be particularly interesting [123].

Natural products have the potential to yield one-of-a-kind molecules and combinations of substances that, in comparison to conventional cancer treatment, have a lower potential for toxicity and a more favorable side effect profile. The work that has been done in drug discovery using natural products has shown that natural compounds display a wide range of biological activities that correlate to anticancer effects. Formononetin (C16H12O4), which derives primarily from red clovers and the herb known as Astragalus membranaceus, native to China. Formononetin induces cell apoptosis (by an intrinsic pathway involving Bax, Bcl-2, and caspase-3 proteins), cell cycle arrest (by regulating mediators like cyclin A, cyclin B1, and cyclin D1), and suppresses cell proliferation (by activating signal transducers and activators of transcription (STAT), phosphatidylinositol 3-kinase/protein kinase-B (PI The AP of both formononetin and the respective drugs can be increased through the use of co-treatment with other chemotherapy drugs such as bortezomib, LY2940002, U0126, sunitinib, epirubicin, doxorubicin, temozolomide, and metformin. This is achieved through a synergistic effect. The accumulation of the evidence that has been gathered up to this point indicates that formononetin has the potential to be a promising candidate for chemoprevention and chemotherapy [124].

**Liu, D., et al.** [125] determined whether or not combined treatments of curcumin and resveratrol were more effective than individual treatments in rat model of lung carcinogenesis. In the course of the research, both biophysical and biochemical parameters were taken into consideration. The rats were divided into five groups: a normal control group, a benzo[a]pyrene (BP) treated group, a BP + curcumin treated group, a BP + resveratrol treated group, and a BP + curcumin +

resveratrol treated group. Each group received a different treatment. According to the findings, there were discernible shifts in the biochemical indices of the rats that had been given BP. In addition, radiorespirometric studies conducted on rats that were given BP demonstrated a significant increase in the rate of 14C-glucose turnover and uptakes. Recording the uptakes of 3H-thymidine in the lung slices of rats that had been treated with BP allowed researchers to indirectly observe a significant increase in the rate of cell proliferation. On the other hand, administration of curcumin and resveratrol together as a dietary supplement to rats that had been treated with BP significantly modulated both biophysical and biochemical index. Histopathological studies provided additional evidence supporting the efficacy of combined treatment with phytochemicals in the prevention of lung carcinogenesis. Author concluded that the combination of curcumin and resveratrol modulated lung carcinogenesis in rats in an effective manner.

Based on the literature, I have selected two medicinal plants, *Etlingera linguiformis* (CAN) of the Zingiberaceae family and *Smilax ovalifolia* (LEX) of the Smilacaceae family and extracted the free and bound phenolic fractions from the leaves. The polyphenolic fractions were tested for anti-proliferative and pro-apoptotic activity against human lung cancer cells, A549, NCI-H522, and NCI-H23 and animal model.