Chapter 9
Bioinformatics Study on Renin Angiotensin in Lung, and Liver Cancer Using Plant-Based Extracts

Haimanti Mondal, Natarajan Chandrasekaran, Amitava Mukherjee, and John Thomas

Abstract Cancer has been one of the leading causes of increasing mortality rate globally. It is the most prominent cause of death worldwide and in most cases incurable if there is delay in its diagnosis. The etiology of cancer is mostly dependent on its exposure to carcinogens consistently. The Renin-Angiotensin system (RAS) plays a significant role in the field of cancer biology that affects the growth of the tumor, and its dissemination either directly or indirectly. Targeting the RAS and by activating the immunostimulatory pathways, the RAS inhibitors (RASi) can enhance cancer immunotherapy by improving cancer treatment. Currently, researchers are more interested in using bioactive compounds from medicinal plants in anticancer therapy since it has no side effects. Plant-derived bioactive compounds having anticancer properties are generally non-toxic or are less toxic. Several phytochemicals have potential anticancer properties with effects on signaling pathways and cellular processes. This review focuses on the RAS in lung and liver cancer. It also highlights the extraction of bioactive compounds having anticancer effects from medicinal plants by using bioinformatic databases to treat liver and lung cancers.

Keywords Renin-angiotensin system · Bioactive compounds · Liver cancer · Lung cancer · Bioinformatics · Databases

Introduction

Angiotensin-converting enzyme (ACE) is the central unit of the Renin-Angiotensin system (RAS). It controls the blood pressure and regulates the volume of body fluids. ACE enhances the blood pressure and thereby, causes the constricting of blood vessels. ACE helps in the hydrolyzation of peptides by removing a dipeptide from C-terminus end.

H. Mondal · N. Chandrasekaran · A. Mukherjee · J. Thomas (✉)
Centre for Nanobiotechnology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu 632014, India
e-mail: john.thomas@vit.ac.in

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The RAS has been viewed as 'Endocrine RAS' due to its association with the endocrine system. It plays a crucial role in regulation of the blood pressure. In the endocrine system of RAS, an enzyme produced by the kidney, renin acts on circulation of the Angiotensinogen (AGT) protein [1]. Renin helps in cleaving the AGT protein by producing a particular fragment of 10 amino acids, Angiotensin I (Ang I). The inactive decapeptide form of Ang I later gets converted to the active octapeptide, Angiotensin II (Ang II) by removal of the His-Leu dipeptide. Ang II binds to its specific cell surface receptors, AT_1 and AT_2, belonging to the seven transmembrane, G-protein receptor superfamily [1]. The AT_1 receptor plays a significant role in mediating the classical actions like sodium retention, cell proliferation and growth, and vasodilation of Ang II. Simultaneously, the AT_2 receptor helps in promoting the apoptosis, inhibiting cell growth, cell differentiation, and vasodilation that may counterbalance the effect of Ang II on the AT_1 receptor [2].

Angiotensin-converting enzyme 2 (ACE2) plays a pivotal role in protecting the inflammation and fibrogenesis of lung and liver [3, 4]. Cirrhosis and advanced level liver fibrosis are the major risk factors resulting in hepatocellular carcinoma (HCC) [5]. In addition, Idiopathic pulmonary fibrosis (IPF) has been reported to be associated with increased risk of lung cancers [6]. The occurrence of dysplastic or atypical changes in the fibrosis may progress to malignancy, thereby, resulting in the development of cancer in the major fibrosis region [7]. ACE2 is one of the most important parts of the RAS.

Both ACE2 and Ang 1-7 provides protection in liver fibrosis against liver injury and progress of cirrhosis [8]. Since RAS participates in regulation of hepatic fibrosis, tissue modelling, and hepatic inflammation post liver injury, the role of ACE2 in liver disease has been of special interest in comparison to other organs. RAS helps in inducing transforming growth factor β1 (TGF-β1) and activating the hepatic stellate cells [9]. The treatment of the liver disease with angiotensin receptor blockers and Angiotensin-converting enzyme inhibitors (ACEIs) can attenuate the progression of fibrosis in human studies [10]. In addition, ACE2 supplementation is reported to prevent bile duct liver fibrosis [4, 10].

Similarly, ACE2 mediated by the effects of Mas oncogene, peptide product of ACE2 known as the ANG1-7 receptor plays a major protective role in diseases related to lungs [3, 11–13]. ACE2 has been reported to be downregulated in fibrotic condition of neonatal and adult human lungs [3, 12, 13]. They also reported a significant reduction of ACE2 and identification of their protective effects in the IPF human lung [3]. They also demonstrated the regulation of ACE2 in the alveolar epithelial survival cells by balancing both proapoptotic Ang II and its antiapoptotic product, Ang 1-7 [14].

HCC being one of the most frequently occurring cancers has a high mortality rate. Several treatment methods have been reported for treating HCC but most of them also have side effects. Alternatively, the use of plant products not only helps in the prevention but also deals with the co-treatment of HCC. Abdel-Hamid et al. [15] reported the results of a study on the management of HCC by using herbal medicinal products. They demonstrated the mechanism of action and pathways involved in the herbal products and also their bioactive molecules involved in the co-treatment as

well as prevention of the HCC. They also reported that these herbal products and their bioactive molecules inhibit the development and progression of liver cancer in various ways including enhancing the effects of several chemotherapeutic drugs, suppressing the chronic inflammation and oxidative stress, protection against the liver carcinogens, and inhibition of metastasis and cancerous cell growth. Another study by Chen et al. [16] reported the anticancer mechanism and the mode of action of the formulations of some Chinese herbal medicines. They reported the efficacy of these herbal medicines as an alternative therapeutic therapy for liver cancers.

A study by Li et al. [17] reported the effect of Traditional Chinese medicine (TCM) in lung cancers, especially non-small cell lung cancer (NSCLC). They demonstrated that TCM has a profound effect compared to other standard treatments in the treatment of lung cancer. Similarly, another study was reported by Chota et al. [18] on the potential treatment of lung cancer by using an African herbal medicinal plant, *Dicoma anomala.*

Yuan et al. [19] reported the role of several bioactive compounds extracted from plant products in the treatment of cancer. They also demonstrated the mechanism and mode of action of their anticancer effect. A recent study by Chavda et al. [20] reported the use of several natural bioactive components in anticancer therapy. They also reported the encapsulation of natural bioactive molecules in several drug delivery methods to improve their anticancer effect. A new drug delivery system that helps in entrapping the natural bioactive compounds was also developed by them.

This present review mainly focuses on the Renin-Angiotensin system (RAS) and also on the enzymes and inhibitors associated with RAS present in both lung and liver cancers. The treatment of lung and liver cancer using the medicinal plant products is also highlighted. This study also reviews the phytochemicals and bioactive compounds extracted from various medicinal plants by the use of bioinformatic databases and tools and their use in the treatment of liver and lung cancers.

Liver Cancer—Hepatocellular Carcinoma

Zhang et al. [21] reported that liver cancers are reported to be ranked sixth worldwide for most incident cases in the year 2020. It is considered to be the third main leading cause of cancer-associated death with 830,180 mortality per year and 905,677 new reported cases approximately. Based on the estimation of the World Health Organisation (WHO) approximately more than 1.3 million individuals are predicted to die from liver cancers by the year 2040 [21].

Among all the primary liver cancers occurring, hepatocellular carcinoma (HCC) is the one which causes tumor in 75–85% cases [22]. HCC is known to be one of the most malignant lethal tumors commonly occurring over the globe. Molecular studies have revealed that the source of HCC is the mature hepatocytes [23]. They are often diagnosed at a late or advanced stage of cancer and hence, there are very limited options available for their effective treatment at that stage [24].

During the past decade, only one systemic drug, Sorafenib has been reported to be clinically to be effective against advanced HCC. It has been approved by the Food and Drug Administration (FDA) and is the standard drug for treating advanced HCC [21].

In recent years, there has been an advancement in the treatment of advanced HCC. Several molecular targeted drugs as well as immune checkpoint inhibitors (ICIs) have been approved as therapeutic drugs for treating advanced HCC. Moreover, Lee et al. [25] reported that a combination of two drugs, bevacizumab and atezolizumab, brought about a significant change in the treatment of advanced HCC. They demonstrated that the incorporation of ICIs into advanced HCC therapies and also their combination with the molecular targeted therapy is emerging as a novel tool in the enhancement of immune responses.

Liver cirrhosis is the most significant risk factor for liver cancers. Although there has been progress in both diagnosis as well as treatment, surgical resection or orthotopic liver transplantation (OLT) is the only cure [23]. Once the degree of differentiation in the liver worsens, the prognosis for liver cancer patients becomes a worse. Hence, restoring the differentiation state may bring about an improvement in the prognosis. The treatment of differentiation of liver cancer is done for reversing the dedifferentiation method of hepatocyte cells to liver cancerous cells by using drugs. Hence, this can be used as a novel treatment tool for HCC in improving the prognosis, reducing the reoccurrence, and restoring the normal characteristics of the liver [23].

Lung Cancer

Lung cancer is considered as the leading cause of the death of cancer patients [26]. Mortality data has been collected and published by the National Center for Health Statistics (NCHS). In the year 2022, approximately 609,360 deaths from cancer and 1,918,030 new cases are projected in the US. Among them, lung cancer has been projected to cause most of the deaths, accounting for 350 deaths each day [27]. Immunotherapy is now a line of treatment for early stages of lung cancer which has drastically changed the quality of care for the patients with metastatic non-small-cell lung cancer (NSCLC) [26].

Slebe et al. [28] reported that currently immune oncology (IO) therapy has become a significant treatment method for patients living with a NSCLC. However, they revealed that only a limited number of patients benefit from this IO therapy. Hence, biomarkers and predictive biomarkers providing insights into the functional biological pathways at tumor microenvironment (TME) level have the capability of elevating the impact of IO therapy. This may lead to the development of improved and novel drug strategies. They also reported that by using several highly-specific radiolabeled tracers, immune positron emission tomography (immunoPET) could provide these biomarkers, to investigate the main targets in TME with immunoPET imaging. In addition, immunoPET has the ability to provide the pharmacodynamic

biomarkers to help in the development of novel drugs and predictive biomarkers to guide in the decision making of innovative and clinical treatment strategies in lung cancer [28].

Angiotensin Converting Enzyme Inhibitors (ACEI)

Angiotensin-converting enzyme inhibitors (ACEI) are drugs that are prescribed mainly for treating heart problems like stroke, heart failure, coronary artery disease (CAD), heart attacks, and others involving high blood pressure (hypertension), hardening of connective tissues and skin (Scleroderma), diabetes, migraines, chronic kidney disease etc. [29, 30]. These drugs help to relax the arteries and veins and lower the blood pressure. The ACE inhibitors block the ACE from converting to Angiotensin II, thus preventing their production in the body. They can narrow the blood vessels and thereby, results in increasing the blood pressure and forcing the heart to work harder.

ACEI includes Captopril, Benazepril (Lotensin), Fosinopril, Enalapril (Vasotec), Lisinopril (Zestril, Prinvil), Perindopril, Ramipril (Altace), Moexipril, Quinapril (Accupril) and Trandolapril. The exact mechanism of action of ACEIs is still not known completely. Although, they interfere with the Renin-Angiotensin-Aldosterone system, the efficacy of ACE inhibitors is indirectly related to renin level in blood.

Hypertension

ACE inhibitors lower both the diastolic and systolic blood pressure mean arterial blood pressure effectively in normotensive and hypertensive subjects [30–32]. These drugs have been reported to have antihypertensive effects in several randomized clinical [33]. The Eighth Joint National Commission (JNC8) in the year 2014 reported evidence-based guidelines to treat hypertension in adults. They recommended ACE inhibitors as one of the four classes of drugs for initial therapy in adults with hypertension [34]. Currently, the guidelines published by the European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) recommend the ACEI as first-line antihypertensive therapeutic drugs. They are mainly recommended for patients with cardiovascular diseases and diabetes mellitus [35, 36]. The ACE inhibitors are proven to be very effective drugs in White race people and less effective in case of Black race people in clinical practice [30].

Post Myocardial Infarction (MI)

Over the past few decades, there have been multiple randomized trials conducted on mortality due to ACE inhibitors post MI [30, 37, 38]. A majority of the trials conducted have reported a remarkable decrease in the mortality rate as well as slow progression of congestive heart failure after the MI patients were treated with ACEI [30, 39]. The clinical practice for patients with heart failure or dysfunctional left ventricle is treatment with ACEI without delay post MI. It is suggested that all the patients be treated with ACEI initially based on the functional assessment of the left ventricle with a review before proceeding further [40].

Heart Failure

ACE inhibitors improve heart failure by lowering the preload, afterload, and systolic wall stress, resulting in increase of cardiac output without much increase in the heart rate [30, 41, 42]. ACEIs play a significant role in excreting salts by reducing the production of antidiuretic and aldosterone hormones, and augmentation of renal blood flow. The ACE inhibitors also reduce cardiac myocyte hypertrophy. Several large, randomized, prospective placebo-controlled trials have been reported since the 1980s. They revealed that patients with heart failure when treated with ACEIs reduces the overall mortality rate with reduction in ejection fraction [30, 43]. They proved that ACEIs also reduce mortality in asymptomatic patients with dysfunction in their left ventricles [30, 44]. Hence, these trials proved that ACE inhibitors can be recommended strongly as first-line therapeutic drugs for patients suffering from heart failure [45].

Diabetes

Due to diabetes mellitus associated neuropathy, the elevation of glomerular capillary pressure and the Renin-Angiotensin-Aldosterone system have been reported to increase the progression of renal dysfunction [30, 46]. A large, randomized, prospective placebo-controlled trial has proved that ACEIs reduce the neuropathy progression in diabetes mellitus insulin-dependent patients. They also reduce the combined endpoints of transplantation, dialysis, and death significantly [30, 47]. Recent recommendations prescribe ACEIs as first-choice therapy in patients with high blood pressure having no history of CAD, which improves the heart function and decreases the incidence of MI [48].

Chronic Kidney Disease (CKD)

ACE inhibitors are the first-line therapeutic drugs used in CKD patients. The effect of ACEI has proved to be more superior compared to placebo-controlled treatment on slowing the CKD progression and reducing proteinuria [49].

Proteinuria or Nephrotic Syndrome

ACEIs have been reported to reduce the glomerular capillary pressure by dilating the efferent arterioles selectively as well as lowering the arterial pressure [30, 50]. The use of ACEIs has been proven to prevent microalbuminuria progression to proteinuria [30, 51]. The ACE inhibitors provide protection for longer duration against proteinuria progression and development. Hence, they maintain stability in renal function in untreated patients with renal function impairment [30, 51].

Post-transplant Glomerulonephritis

The use of ACEIs is the mainstay and first-line drug in patients suffering from glomerular diseases. It gradually slows down the decreasing proteinuria and glomerular filtration rate (GFR) [30, 52]. Moreover, the Renin-Angiotensin-Aldosterone inhibitors can prolong the survival of graft in patients suffering from post-transplant glomerulonephritis [30, 53].

Bioinformatics Study on Angiotensin Enzymes in Liver and Lung Cancer

Bioinformatic Tools Used in Lung Cancer

Patients with lung cancer are reportedly more susceptible to severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection that began spreading during the Coronavirus disease 2019 (COVID-19) pandemic. The SARS-CoV-2 virus enters the host's body through the Angiotensin-converting enzyme 2 (ACE2) receptor. Samad et al. [54] reported the identification of ACE2 protein as a potential biomarker in the SARS-CoV2 infection and its association with lung cancer by using bioinformatic tools and computational analyses.

ACE2 Expression Analysis Using the Cancer Genome Atlas (TCGA) Datasets

ACE2 transcriptional expression analysis was explored in multiple cancers by applying an online server tool, Gene expression profiling interactive analysis 2 (GEPIA2) that is available publicly using the datasets, "The cancer genome atlas (TCGA)" [55]. They studied the data of mRNA expression of ACE2 gene in lung cancer using TCGA dataset through UALCAN website [56, 57]. Further, they analyzed the mRNA expression of the ACE2 gene using another tool, Oncomine and the TCGA datasets [58, 59]. Both web-platforms, UALCAN and Oncomine are user friendly and are used for revealing the gene expression of the TCGA data and also relative expression of a particular query gene set.

Mutational and Survival Analyses of AEC2 Gene in Lung Cancer

The Genotype 2 outcome server was used to perform the survival analysis of the AEC2 gene in lung cancer. This server provides Kaplan–Meier plots using TCGA data. The position of mutational analysis was performed using cBioPortal in lung cancer through TCGA data [60].

COVID-19 Gene Identification and Co-expression Profiling of AEC2 Gene Using the Comparative Toxicogenomics Database (CTD)

The co-related genes of lung squamous carcinoma (LUSC) and lung adenocarcinoma (LUAD) in Visualization platform and R2 genomics analysis were collected using the TCGA dataset [61]. Then using the comparative toxicogenomics database (CTD) all the COVID -19 genes were downloaded [62] in text format and visualized by FunRich software.

Protein–Protein Interaction Using the GeneMANIA Database of Co-expressed Genes

An extensive database, GeneMANIA was used that provided a flexible interface for the gene function, proteomic, and genomic data query. This database has functional associated data that includes co-expression, gene and protein interactions, and pathways [63, 64].

Gene Ontology Analysis and Functional Pathway of Common Co-related Genes with COVID-19 Associated Lung Cancer

Kyoto encyclopedia of genomes and gene (KEGG) database is used for high-level function and biological system utilities through high-throughput technologies and information related to genome sequencing at molecular level [65]. Gene ontology analysis was predicted for computation of biological system. Gene ontology was performed by using web portal, Enrichr. In addition, the analysis of commonly co-related genes of the COVID-19 pandemic and lung cancer was done for their enrichment functional pathway [66].

Bioinformatic Tools Used in Liver Cancer

ACE2 is the SARS-CoV-2 receptor causing COVID-19 pandemic and Transmembrane serine protease 2 (TMPRSS2) is the coreceptor. The abnormality in the hepatic function due to COVID-19 infection suggested bystander or specific liver disease. The liver cells are widely used as SARS-CoV-2 infection models in vitro since they can express the viral ACE2 receptor. Desquilles et al. [67] demonstrated the analysis of TMPRSS2 and ACE2 expressions and their localization in non-tumorous livers and human cancerous livers. They reported that the differentiated liver cancers displayed the potential relation between metabolic breakdown and dysfunction of AEC2 gene using transcriptomic datasets.

Datasets Used in HCC Liver Cancers

The Désert's microarray meta dataset was used. This is composed of many human HCCs. In this particular dataset, the HCCs that express an activated β-catenin transcriptomic program was identified with 5 genes including LGR5, VNN1, GHUL, HAL and ODAM, predicting activated Catenin-β1 (CTNNB1) mutations with specificity as well as high sensitivity [68]. The TCGA dataset was composed of many HCCs and non-tumorous samples. The methylation, RNA sequencing and mutation data were extracted using TCGA Abiolinks R package [68].

Plant Extracts for Treating ACE in Liver and Lung Cancer

Plant Extracts for Treating ACE in HCC

Bioactive compounds obtained from plant products have been successfully tested for treating the HCC as an alternative to chemotherapeutic drugs. The bioactive molecules from plants reported for treating liver cancer are listed in Table 9.1.

Plant Extracts for Treating ACE in Lung Cancer

Plant extracts have been reported to give significant results when used for treatment of several disorders either acute or chronic, and even cancer of the lungs. Bioactive compounds reported from plants for treating lung cancer are listed in Table 9.2.

Bioinformatics Work Using Plant Extracts for Treating Lung and Liver Cancer

A meticulous and detailed search has been performed on several electronic databases including PubMed, Scopus, Google Scholar, and Web of Science to retrieve relevant literature. A proper and detailed query set was designed on the databases. During the search, all the phrases, keywords, and relevant terms were used including "Natural medicinal plants," "Lung cancer," "Liver cancer," "carcinoma," "cancerous," "hepatocellular carcinoma," "Anticancer," "Anticancer plants;" "Anticancer herbs," "Renin-Angiotensin," "Angiotensin-converting enzymes," "in vivo activity," "in vitro activity," and "Animal models" [69].

The number of articles found to be relevant to our search were finalized. The data obtained after the curation, analysis, and extraction through the designing of phrases/keywords combination with their inclusion criteria were noted [69].

The inclusion criteria were based on two sets. The first set of criteria is the 'general criteria'. In this criterion, the articles chosen for the manuscript had reported both the anticancer activity of traditional plants and the anticancer role of pure compounds or their extracts from the plants. The second criteria included the selection of specific plants having anticancer properties with a detailed list of phytochemicals present in them. Articles in current journals on the anticancer activity of relevant plants were selected. The in vivo and in vitro anticancer activities of the medicinal plants and the antitumor/anticancer activities of the bioactive compounds extracted from them was reported [69].

An in-silico study by Putra et al. [70] reported on the anticancer potential of several Indonesian herbal plants. They first used databases like Pubchem, Protein data bank (PDB), Marvin Sketch software, and Ramachandran plot to retrieve the

Table 9.1 Bioactive compounds from plant extracts for treating liver cancer (HCC)

S. No.	Plants	Bioactive compounds	References
1	*Zingiber officinale* (ginger)	Zingerone, 6-gingerol, 6-shogaol, zerumbone	[71]
2	*Curcuma longa* (turmeric)	Curcumin	[72]
3	*Allium sativum* (garlic)	Allicin, diallyl sulfide, diallyl disulfide, S-allylcysteine	[73, 74]
4	*Ferrula asafoetida* (asafoetida)	Ferulic acid, Farnesiferol A, Umbelliferone	[75, 76]
5	*Cinnamomum verum* (cinnamon)	Cuminaldehyde, 2-methoxy-cinnamaldehyde	[77, 78]
6	*Crocus sativus* (saffron)	Crocin, α-carotene, β-carotene, lycopene	[79–81]
7	Cruciferous vegetables like *Brassica oleracea* var. *capitata* (cabbage), *Brassica oleracea* var. *italica* (broccoli), *Raphanus sativus* (radish), *Nasturtium officinale* (watercress), *Brassica rapa* (turnip), *Lepidium sativum* (garden cress), *Brassica oleracea* var. *sabellica* (kale)	Benzyl isothiocyanate, phenethyl isothiocyanate, allyl isothiocyanate, DL-Sulforaphane, indole-3-carbinol	[82–85]
8	*Coffea* sp. (coffee)	Caffeine	[86–90]
9	*Camellia sinensis* (tea)	Catechins, flavins, epigallocatechin gallate	[91–95]
10	*Taraxacum officinale* (dandelion)	α-amyrin, β-amyrin, taraxasterol, lupeol	[96]
11	*Solanum lycopersicum* (tomato)	Lycopene, α-tomatine	[97]
12	*Allium cepa* (onion)	Quercetin	[98–100]
13	*Punica granatum* (pomegranate)	Cuanidin-3,5-O-diglucoside, pelargonidin, delphinidin, gallic acid, ellagic acid, urolithin A	[102–104]
14	*Malus domestica* (apple)	Chlorogenic acid, Phloretin, Proanthocyanidin B2, epicatechin, catechin, rutin, maleic-acid styrene	[105, 106]
15	*Fragaria ananassa* (strawberry), *Vitis vinifera* L. (grapes)	Fisetin	[107]
16	*Vaccinium* sect. Cyanococcus (blueberries, tree wood, grapes	Pterostilbene	[108, 109]
17	*Arachis hypogaea* (peanuts), grapes, red wine, *Pinus* sp. (pines)	Resveratrol, tanshinone I, Tanshinone IIA, β-elemene, Emodin, Aloe-emodin	[110–112]
18	*Panax Ginseng* (ginseng)	Ginsenosides, Protopanaxadiol (PPD)	[113–116]

(continued)

Table 9.1 (continued)

S. No.	Plants	Bioactive compounds	References
19	*Citrus reticulata* (tangerine)	Tangeretin	[113–115]
20	*Amaranthus spinosus* (spiny amaranth)	(14E, 18E, 22E, 26E)-methylnonacosa-14, 18, 22, 26 tetraenoate	[117]
21	*Ziziphus jujuba* (jujube)	Ursolic acid, Oleanolic acid	[118–120]
22	*Diospyros kaki* (persimmon)	Flavonoids and non-specified terpenoids	[121]
23	*Digitalis ferruginea* (rusty foxglove)	Lanatoside C	[122]
24	*Astraeus hygrometricus* (hygroscopic earthstar)	Astrakurkurone	[123]
25	*Artemisia annua* (sweet sagewort)	Artemisinin	[124, 125]
26	*Scutellariae radix* (Scutrllaria)	Oroxylin A	[126, 127]
27	*Fagopyrum tataricum* (tartary buckwheat)	Tatariside F	[128]
28	*Garcinia mangostana* (mangosteen)	Mangostanaxanthone V and VI, α-mangostin	[129]
29	*Nelumbo nucifera* (sacred lotus)	Neferine	[130]
30	*Rhizoma coptidis* (Huang Lian)	Berberine	[131]
31	*Alpinia galanga* (galangal)	Acetoxychavicol acetate	[132]
32	*Glycyrrhiza glabra* (licorice)	Glabridin	[133, 134]

Hassan [115], Rodriguez et al. [116], Rawat et al. [135]

protein and ligand. They later performed molecular docking by using the AutoDock tools software, and visualized the docking analysis using the Discovery Studio 4.0 for evaluating the binding value of Gibbs free energy and their amino acid residues. They reported three bioactive compounds, physcionin, berberine, and pinostrobin that showed potential anticancer properties against the lung cancer.

Conclusion

Cancer, being a public health problem has a profound impact on the health of people in both developing and developed countries across the globe. Clinical studies provided enough compelling evidences that Ang II helps in regulating all the hallmarks of several cancers, including liver and lung cancer. To overcome the problems involved in the use of currently available drugs for the treatment of cancer, there is a need to look for certain effective and novel anticancer agents that can improve the efficacy with minimum side effects. In the present review, bioinformatic databases were used to obtain the potential bioactive compounds from medicinal plants to treat lung and liver cancers. Later, anti-cancerous as well as bioactive medicinal compound

Table 9.2 Bioactive compounds from plant extracts for treating lung cancer

S. No.	Plants	Bioactive compounds	References
1	*Angelica keiskei* Koidz	Xanthoangelol E	[136]
2	*Erythrophelum succirubrum*	Pyrogallol; Resorcinol; β-glyceryl monostearate; ethyl linoleate; 2,6-Diphenylimidazol[1,2-b]-[1,2,4]-triazine; ethyl hexadecanoate; ethyl gallate	[137]
3	*Psoralea corylifolia* (babchi)	4′-O-methylbavachalcone	[138]
4	*Nigella sativa* (black cumin)	α-hederin	[139, 140]
5	*Alnus japonica* (Japanese alder)	Hirsutenone	[141]
6	Chili	Capsaicin	[142]
7	*Polygonum* sp. *Rheum* sp.	Emodin	[143]
8	*Bridelia ovata*	Palmitic acid; Friedelan-3-one; Citrostadienol; Fucosterol; Epifriedelanol; 1-Tricosene; Elemicin; Petroselinic acid; Hebesterol; Stigmast-5-en-3-ol; α-Tocopherol	[137]
9	*Rheum officinale* (Chinese rhubarb)	Emodin	[144]
10	*Salvia rosmarinus* (rosemary)	Carnosic acid	[142]
11	*Petroselinum crispum* (parsley), *Citrus paradasi* (grapefruit), *matricaria chamomilla* (chamomile), *Citrus sinensis* (orange), tea, onion, wheat sprouts	Apigenin	[145]
12	*Paulownia tomentosa*	Tomentin E	[146]
13	*Salvia miltiorrhiza* (danshen)	Cryptotashinone, Dihydrotanshinone I	[147]
14	*Dendrobium pulchellum*	Chrysotoxine	[148–150]
15	*Dracocephalum rupestre*	Eriodictyol	[151]
16	*Ecklonia cava* (marine brown algae)	Dieckol	[152]
17	*Piper nigrum* (pepper), *Apium graveolens* (celery), *Mentha piperita* (peppermint), *Thymus vulgaris* (thyme), *Lonicera caprifolium* (honeysuckle)	Luteolin	[153]

(continued)

Table 9.2 (continued)

S. No.	Plants	Bioactive compounds	References
18	*Croton oblongifolius*	Benzoic acid; Kaur-16-en-18-oic-acid; Stigmast-5-en-3-ol; Aflatoxin G1	[137]
19	*Uncaria tomentosa* (cat's claw)	Mitraphylline	[154]
20	*Tanacetum parthenium* (feverfew)	Parthenolide	[142]
21	*Azadirachta indica* (neem)	Nimbolide	[142]
22	*Tribulus terrestris* L. (gokshur)	Terrestrimine, Lianhuaqingwen, Herbacetin, Rhoifolin, Pectolinarin	[155–157]
23	*Vanilla planifolia* (flat-leaved vanilla)	Vanillin	[158, 159]
24	*Aglaia perviridis*	Myricetin	[160]
25	*Triterygium regelii* (Regel's threewingnut)	Tingenone	[161]
26	*Torreya nucifera* L. (Japanese nutmeg-yew)	Amentoflavone	[161]
27	*Scutellaria baicalensis* (Chinese skullcap)	Scutellarein	[160]
28	*Sambucus javanica* (Chinese elder)	Gallic acid, chlorogenic acid, caffeic acid	[162]

Poofery et al. [137], Benarba and Pandiella [163], Rahman et al. [164]

libraries from several endemic plants from different regions can be developed by using high-throughput techniques.

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