Natural Products from Mangrove - Potent Inhibitors of Lung Cancer

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ABSTRACT

Cancer is the major cause of human mortality in the world and lung cancer remains the most common cause of cancer mortality worldwide. Chemotherapeutic drugs are still considered as the most important treatments for cancer, however, they trigger enormous adverse effects. Ongoing research on natural medicinal sources is receiving greater attention due to their lower adverse effects. Natural products have been the major source of the currently available anticancer drugs, and identifying their active chemical ingredients is viewed as an attractive approach for drug development. Natural products derived from plants with anticancer properties have been classified as alkaloids, aldehydes, terpenoids, glycosides, lignans, lipids, unsaponified lipids, nucleic acid, polysaccharides and proteins. Among many plants Mangrove are considered to be rich sources of steroids, triterpenoids, saponins, flavonoids, alkaloids and tannins. Mangrove based plant drugs have shown remarkable outcome in prevention of lung cancer and lung metastasis. The present idea may reveal the significance of the discovery of new novel mangrove plant based drugs essentially for lung cancer in the foreseeable future.

Keywords: Mangrove, natural products, lung cancer, pyrazole, Rhizophora apiculata, anti-cancer agents.

1. INTRODUCTION

Lung cancer is the most common cause of cancer related deaths in men and women, and was responsible for 1.66 million deaths worldwide annually, as of 2012, making lung cancer the leading cause of cancer-related mortality [1]. There are 1.61 million new cases of lung cancer globally per year [2] and it kills more people than colon, breast, and prostate cancers [3]. Lung cancer is responsible for 17.8% of all cancer deaths [4]. Lung cancer is majorly divided into small cell (small round cells in the lung) lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (cells grow inside the lung other than the small cells). In 2011, NSCLC remained the principal cause of cancer-related deaths worldwide accounting for more than one million deaths per year [5,6].

The major risk factor for developing lung cancer is tobacco use and thus, this disease is often viewed solely as a smoker's disease. However, a significant number of patients with lung cancer have no history of smoking. Globally, lung cancer in non-smokers demonstrates a marked gender bias, occurring more frequently among women. In particular, a high proportion of Asian women diagnosed with lung cancer are non-smokers. Although smoking-related
Natural Products with Anticancer Properties

Medicinal plants occupy an important position for being paramount sources of drug discovery. Though there are a number of plants available with anticancerous properties, continuous effort has been given for the search of drugs from novel natural plant origin which have limited adverse effects [14,15]. Natural products derived from plants with anti-cancer properties have been classified as alkaloids, aldehydes, terpenoids, glycosides, lignans, lipids, unsaponified lipids, nucleic acid, polysaccharides and proteins [14]. Secondary metabolites from plants sources have been used as source of traditional medicine in ancient days. Natural compounds such as alkaloids, phenolic compounds, steroids and terpenoids are a few secondary metabolites that have pharmacological and toxicological activity [16-23]. Many reports have revealed that the products isolated from marine environment had unique structural features not found in terrestrial natural products [22-23].

3. Mangrove and their anticancer properties

Mangroves are among the world’s most productive ecosystems. They enrich coastal waters, yield commercial forest products, protect coastlines, and support coastal fisheries. However, mangroves exist under conditions of high salinity, extreme tides, strong winds, high temperatures and muddy, anaerobic soils. There may be no other group of plants with such highly developed morphological, biological, ecological and physiological adaptations to extreme conditions. Mangroves and mangrove ecosystems have been studied extensively but remain poorly understood. With continuing degradation and destruction of mangroves, there is a critical need to understand them better [24]. As researchers continue to discover important facts about mangroves and the role they play in the global ecosystem, the volume of published information has grown enormously and increasing numbers of workers are drawn to these unique environments. Mangroves are distributed circumtropically, occurring in 112 countries and territories. Global coverage has been variously estimated at 10 million hectares [25] and 18 million hectares, with 41.4% in south and Southeast Asia and an additional 23.5% in Indonesia. In India, Pichavaram Mangroves is situated in the southeast coast of India, south of Cuddalore. Pichavaram forms a great wealth of biological diversity in mangrove ecosystem. The mangroves are distributed in varying degree of abundance, in which A. marina is the most common species followed by R. apiculata, R. mucronata, Bruguiera cylindrica and Aegiceras corniculatum.

Mangroves have numerous amounts of medicinal plants and only a few have been explored. Mangrove plants which are reported to have potent anticancer activity are such as Acanthus illicifolius [26], Acanthus ebracteatus [27], Acrostichum aureum [28], Aegiceras corniculatum [29], Avicennia africana [30], A. nitida [31], Avicennia alba [29], A. marina [32], Bruguiera exaristata, Bruguiera Sexangula, [33], Barringtonia asiatica [34], Bruguiera cylindrica [35], Bruguiera gymnorrhiza [28], Ceriops tagal [36], Calophyllum inophyllum [37], Excoecaria agallocha [38], Heritiera fomes [39], Ipomea pes-caprae [40], Lumnitzera racemosa [41], Nypa fruticans [42], Pandanus odoratissimus [43], Phoenix paludosa [44], R. mucronata [45],
R. apiculata [46], Sonneratia apetala [47], Suaeda maritima [48], Sarcolobus globosus [49], Sonneratia alba [50], Stenochlaena palusiris [51], Terminalia catappa [52], Xylocarpus granatum [53], Wedelia biflora [54,55] and Avicennia officinalis [56].

4. Therapeutic potential of mangroves against lung cancer

4.1. Acanthus ilicifolius

Acanthus ilicifolius (Acanthaceae) has received substantial attention due to its wide range of secondary metabolites and its traditional usage in Indian and Chinese system of medicine. Acanthus ilicifolius survives in the most hostile environment with fluctuating tidal and saline regime. These plants are considered to be rich sources of steroids, triterpenoids, saponins, flavonoids, alkaloids, and tannins [26]. The plant Acanthus ilicifolius is reported to have anticancer activity and the alcoholic extract of this plant has cytotoxicity towards lung fibroblast (L-929) cells [57,58].

4.2. Excoecaria agallocha

Excoecaria agallocha L., (E. agallocha), belonging to the family Euphorbiaceae, is widely distributed on seashores and edge-mangroves throughout tropical Africa, Asia and northwest Australia. The plant is known to play an important economical, ecological as well as medicinal role. These plants are considered to be rich sources of diterpenoid, triterpenoid derivatives and alkaloids and diterpenes extracted from the plant were also found to possess anti-tumour promoting activity [59]. Ethanol extract of E. agallocha is reported to have anticancer effect on human lung cell line which has shown significant inhibition over human lung cancer cell growth, cell cycle progression and induced apoptotic cell death in human lung cancer cell lines. The plant extract of E. agallocha inhibited the proliferation of lung carcinoma cells in a dose-dependent manner and caused apoptotic programmed cell death in p53+/+ cells and p21-mediated G1 arrest in p53-/- cells. The molecular mechanism of induction of apoptotic cell death in lung cancer cells are mediated by p53, Bcl-2, Bax-dependent cell apoptotic pathways [60].

4.3. Avicennia marina

A. marina, commonly known as grey mangrove or white mangrove, is a species of mangrove tree classified in the plant family Acanthaceae and as with other mangroves, it occurs in the intertidal zones of estuarine areas. Previous findings reveal that methanolic extract of A marina has higher concentrations of pentanoic acid, decanoic acid, diethylhdroxylamine, pyrrolidine, 4-chlorophenyl, thiazolidinones and arabinopyranoside (flavonoid) [61]. A marina has been used as traditional medicine for years because of its variety of biological activities, such as anti-bacterial, anti-inflammatory, antifungal, anti-atherosclerotic, anti-tuberculosis, anticonvulsant, anti-aging, anti-cholinergic, anti-ulcer, anti-cancer, anti-plasmodial, antioxidant, and anti-tumor properties [62-64].

4.4. Sesuvium portulacastrum

Sesuvium portulacastrum (S. portulacastrum) is a sprawling perennial herb that grows in coastal areas throughout the world. Sesuvium portulacastrum grows in sandy clay, coastal limestone and sandstone, tidal flats and salt marshes. It is native to Africa and Asia. S. portulacastrum is reported to have antioxidant, anti-microbial and anti-cancer properties. Bioactive compounds were found in the leaf of callus. Seven phytochemicals that were identified in the extract were further subjected to molecular docking analysis against lung and oral cancer proteins by using the Argus Lab software. Among the seven compounds, hexadecaenoic acid, 2 [octadecyloxy] ethyl ester was the most potent. Phytochemicals which exhibited a strong interaction and binding with oral cancer and lung cancer proteins. The extracts also contain hydroxyl group compounds such as phenols, flavonoids and other volatile substances which reported to have significant antioxidant activities. Therefore mangroves are promising source of bioactive compounds to develop drugs against lung cancer [65].

4.5 Rhizophora apiculata

Rhizophora apiculata, in the family Rhizophoraceae, is an important plant used in traditional medicines by many people in Asia and Africa. The healing properties attributed to the R. apiculata tree in folk medicine are based, to a great extent, on the fact that use of root, leaf, and/or stem extracts impart an inhibitory effect on the growth of human bacterial, viral, and fungal pathogens [66]. A polysacchride extracted from the leaf of R. apiculata inhibited HIV-1 or HIV-2 strains in various cell cultures [67].

Our earlier studies revealed that R. apiculata extract was an effective immunostimulant and chemoprotectant against cyclophosphamide-induced toxicity in experimental animals [68]. Also we had
reported that *R. apiculata* possessed effective antitumor property against B16F10 melanoma cells [69]. *R. apiculata* was also evaluated for its lung metastasis inhibition using the B16F-10 melanoma induced lung metastasis model in C57BL/6 mice and we have reported that *R. apiculata* extract (10 mg/kg b.wt (intraperitoneal) significantly inhibited pulmonary tumor nodule formation (41.1 %) and also increased the life span (survival rate) of metastatic tumor bearing animals. The administration of *R. apiculata* extract significantly reduced biochemical parameters such as lung collagen hydroxyproline, hexosamine, uronic acid content, serum nitric oxide (NO), γ-glutamyl transpeptidase (GGT) and sialic acid levels when compared to metastasis controls. These results correlated with lung histopathology analysis of *R. apiculata* extract treated mice showing reduction in lung metastasis and tumor mass. These anti-metastasis activities could be attributed to the high content of 4-pyrrolidinyl, pyrazole, ketone derivatives and thiazolidine-diones found in the methanolic extract of *R. apiculata*. [69]. Taken collectively, *R. apiculata* extract could be used as a potential anti-metastasis agent against lung cancer.

### 4.6 Terminalia catappa

*Terminalia catappa* L. is a combreteaceous plant broadly distributed on tropical and subtropical beaches. The leaves, bark and fruit of *Terminalia catappa* have been used for treating dermatitis and for antipyretic and homeostatic purposes in India. *Terminalia catappa* are rich in flavonoids and hydrolysable tannins such as punicalagin, punicalin, terflavins A and B, tergallagin, tecatain, geraniin, granatin B, corilagin [70]. *Terminalia catappa* leaf extract (TCE) was reported to have inhibitory activity on the invasion and motility of highly metastatic A549 and Lewis lung carcinoma (LLC) cells. A549 and LLC cells were treated with *Terminalia catappa* leaf extract at various concentrations, up to 100 µg/mL, and were reported to decrease the expressions of matrix metalloproteinase-2, -9, urokinase plasminogen activator and their endogenous inhibitors, that is tissue inhibitor of metalloproteinase-2 and plasminogen activator inhibitor-1. Therefore, *Terminalia catappa* leaf extract could be applied to be a potential antimetastatic agent. TCE is also reported to inhibit tumor growth and lung metastasis in C57BL/6 mice [70]. TCE has an inhibitory potential against invasion and metastasis of A549 cells in vivo without showing any apparent sign of toxicity as proved by MTT assay. TCE exerted an inhibitory effect on several essential steps of metastasis, including cell invasion and motility. In addition, TCE could regulate the activities of invasion-associated proteases and their natural inhibitors. As evidenced from above results, TCE may be a powerful candidate in developing preventive agents for cancer metastasis.

### 5. CONCLUSION

Although numerous plants from mangroves are broadly used in traditional medicine, only few have been assessed for biological activities and have been studied for their potential anti-cancer properties but limited number of mangrove plants that have been examined for their activity against lung cancers. This review underlines the use of novel, natural mangrove plant- based drugs for cancer treatment, mainly for lung cancer. We have shown that mangrove based plant drugs have remarkable activity in prevention of lung cancer and lung metastasis. This review will provide a wide idea and could reveal the significance of the discovery of new novel mangrove plant-based drugs, essentially for lung cancer, in the foreseeable future.

**Conflict of Interest**

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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