Chapter 13
Anticancer Potential of Mangrove Plants: Neglected Plant Species of the Marine Ecosystem

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13.1 Introduction

Cancer is a complex form of disease which is responsible for a significant number of mortalities worldwide. It is characterized by the uncontrolled growth and spread of abnormal (unresponsive to cellular signaling) cells within or out of the tissue, resulting in accumulation, local damage, and inflammation (ACS 2016). According to WHO (2017), cancer is one of the leading causes of infirmity and fatality globally, with 8.8 million deaths in the year 2015. Common forms of cancer mortality are lung cancer (1.69 million deaths), liver cancer (788,000 deaths), colorectal cancer (774,000 deaths), stomach cancer (754,000 deaths), and breast cancer (571,000 deaths). Lung cancer (bronchogenic carcinomas) is the most common cancer among men and the ninth most common among women, whereas breast cancer remains the leading cause of cancer mortality among women (Ferlay et al. 2015; Torre et al. 2015). It has been predicted that, by the year 2030, the number of newly diagnosed cancer cases will increase globally to 21.7 million and 24 million by 2035 with about 70% of mortalities mostly occurring in low- and medium-income countries

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M. S. Akhtar, M. K. Swamy (eds.), *Anticancer Plants: Properties and Application*,
https://doi.org/10.1007/978-981-10-8548-2_13

such as Africa, Asia, and Central as well as South America (Ferlay et al. 2015). The major causes accounting for more than one-third of deaths from cancer are due to the behavioral and dietary risks such as obesity, poor intake of fruit and vegetable, physical inactivity, tobacco, and alcohol consumption, while tobacco consumption alone is responsible for about 22% of cancer deaths worldwide. Cancer-causing infections, such as hepatitis and human papilloma virus (HPV), are also responsible for about 25% of cancer cases in low- and middle-income countries (Plummer et al. 2016).

Current treatment for different forms of cancer are carried out through surgeries, radiation therapy, and/or systemic therapies such as chemotherapy, hormonal therapy, neoadjuvant therapy, immune therapy, gene therapy, and targeted therapy. These treatments may be used alone or in combination depending on the cancer type and its stage, tumor characteristics, and the patient's age, health, and preferences. Some of the therapies are performed through supportive therapies to reduce side effects and address other patient and family quality of life concerns (ACS 2016; Yue et al. 2017). However, despite the availability of a number of treatments, many forms of cancers still remain intractable, which may be either due to delays in identification, diagnosis, sophistication, or high treatment cost. The current experimental therapy for cancer is highly sophisticated and costly and has low satisfactory outputs. Moreover, in such therapies if approved by FDA due to their serviceability, the high cost would make these treatments practically unaffordable for the use of common people in low- and middle-income countries. Henceforth current research is directed toward evaluating simpler or greener treatment of cancer, which includes the use of natural products/herbal medicines (Yin et al. 2013). Some of the conventionally used plants with anticancer properties are ginko, goldenseal, ginseng, garlic, *Echinacea*, jivanti, aloe vera, big sage, and saw palmetto (Swamy et al. 2015a; Shareef et al. 2016; Mohanty et al. 2017). Furthermore, recent researches are more focused on finding therapeutics with anticancer activity from plants of terrestrial origin, because of their easy accessibility. One such potential candidature is represented by the plants from the mangrove ecosystem, considering their rich phytochemicals, their bioactive compounds, and their unique ability to thrive in harsh environmental conditions and ethnobotanical significance (Vannucci 2000; Dissanayake and Chandrasekara 2014; Mahmud et al. 2014).

Mangrove ecosystems are marginal ecosystems inhabiting the estuarine and intertidal regions or the interface between land and sea in both tropical and subtropical latitudes confined largely to regions between 30° north and south of the equator (Vannucci 2000; Das et al. 2014). There are approx. 1,59,041.5 km^2 of mangrove forests distributed in 123 countries and territories all over the world (Saranraj and Sujitha 2015). As reported by Das et al. (2014), there are 74 true mangrove plant species within 27 genera, which belong to 20 families dispersed through the world (Kathiresan and Bingham 2001; Ward et al. 2016). There are also an innumerable numbers of bacteria, fungus actinomycetes, mollusks, etc. that together enrich the biodiversity of the mangrove ecosystem. Mangrove forests occur in rough environmental conditions such as high salinity, high temperature, muddy anaerobic soils, extreme tides, and strong winds, which fluctuate violently

and frequently (Vannucci 2000). The capability of these organisms to resist the biotic or abiotic stresses and survival are attributed to their adaptability/tolerance toward a hostile ecological condition through alterations in physiological processes resulting from several novel bioactive products like hormones, antioxidants, secondary metabolites, resistant proteins, and sterols (Bandaranayake 2002; Edreva et al. 2008; Mangamuri et al. 2016; Sofia and Teresa 2016; Prasannan et al. 2016; Basha and Rao 2017). A number of bioactive compounds from mangrove plants have substantial pharmacological properties and are being used traditionally for medication against several health disorders and ailments (Edreva et al. 2008). The therapeutic extracts of roots, barks, leaves, fruits, and cell-free extracts of the microbes have been evaluated for various ethnomedicinal uses for the complete/partial treatment of malaria, filaria, inflammation, dysentery, diarrhea, cholera, lung infection, gastrointestinal infection, metabolic disorders, etc. (Sosovele et al. 2012; Gopal et al. 2016; Thatoi et al. 2016a; Mendhulkar et al. 2017). Despite the abundant contents of bioactive compounds with diversified therapeutic activities, mangrove species had not been efficiently explored to their maximum potential till date. However, the in vitro and in vitro anticancer activities of few mangrove plants have been evaluated, despite their extensive bioactive compound profiling (Huang et al. 2016).

Various plant extract-mediated nanoparticles have been proved to possess biological significance with antimicrobial, antioxidant, and anticancer properties (Swamy et al. 2015b; Swamy et al. 2015c; Akhtar et al. 2015; Rudramurthy et al. 2016). It has been postulated that conjugation of bioactive metabolites from mangrove sources with nanoparticles can boost the molecular properties and efficiency of the compounds as a promising therapeutic agent against cancer as well as other health issues. Considering the idea as true, the present chapter focuses on the anticancer activities of mangrove species, specifically phytocompounds and their bioconjugation with nanoparticles or nanocarriers as an advanced therapeutic agent. This comprehensive information will certainly benefit cancer biology researchers and pave a way for developing a smart and efficient therapeutics against different forms of cancer.

13.2 Distribution of Mangroves in the World

Mangrove plants are distributed in 123 tropical and subtropical countries around the world comprising of 74 true mangrove species including trees, shrubs, palms, and ferns. Higher percentages of the world's mangrove ecosystem can be found in Asian and African countries followed by America (South and Central). Sundarbans of India and Bangladesh covers the largest continuous mangrove forests consisting more than 0.14% of the geographical area of the country (Kathiresan 2010; Sarker et al. 2010). Mangroves are distributed in West and Central Africa, East and South Africa, Australia and New Zealand, South Asia, North and Central America, South America, Southeast Asia, the Pacific Ocean, the Middle East, and East Asia (Spalding et al. 2010).

In South and Southeast Asia, mangroves are found in Indonesia (60%), Malaysia (11%), Myanmar (8%), Papua New Guinea (8%), and Thailand (5%). Twenty-one species out of 35 mangrove plants in Southeast Asia are rare (*Sonneratia caseolaris*, *Sueda fruticosa*, *Urochondra setulosa*, etc.). In Western and Central Africa, 17 species of mangrove plants are found including *Avicennia marina*, *Rhizophora mucronata*, *Bruguiera gymnorrhiza*, *Ceriops tagal*, *Lumnitzera racemosa*, and *Rhizophora mucronata.* Forty-five mangrove species have been recorded from Australia and New Zealand (Webber et al. 2016). The North and South America comprising Florida and the Bahamas, Mexico, Puerto Rico, Eastern Venezuela, Trinidad, Guiana, and Brazil can be found with mangrove ecosystem. Brazil comprises 15% of the mangrove forest in this region. *R. mangle*, *Laguncularia racemosa*, *Avicennia germinans*, and *Conocarpus erectus* are common in Mexico. Mangrove forests can be seen in the Arabian Peninsula, Red Sea, and Gulf regions (Bahrain, Qatar, UAE, and Oman). Four species of mangrove plants such as *A. mariana*, *R. mucranta*, *Ceriops tagal*, and *B. gymnorrhiza* are observed in the Middle East area (Giri et al. 2011; Singh et al. 2012).

13.3 Diversity of Mangrove Species

Mangroves can be broadly categorized into two groups, i.e., exclusive/ major mangrove species (also called strict/obligate/true mangroves) and non-exclusive/minor/ associate mangrove species (Tomlinson 1986). The major species are the strict or true mangroves. The minor mangrove species are less conspicuous elements of the vegetation and rarely form pure stands which mostly involve different endophytes. Mangrove-associated microbes include bacteria (*Desulfovibrio*, *Desulfotomaculum*, *Desulfosarcina*, *Desulfococcus*, *Azotobacter*, *Staphylococcus*, and *Pseudomonas* species), fungi (*Aigialus striatispora*, *Calathella mangrovei*, *Eutypa bathurstensis*, *Falciformispora lignatilis*) and fungus-like protists (*Halophytophthora vesicula* and *H. spinosa*), microalgae (*Coscinodiscus*, *Rhizosolenia*, *Chaetoceros*, *Biddulphia*, *Pleurosigma*, *Ceratium*, and *Protoperidinium*), macroalgae (*Bostrychia*, *Caloglossa*, and *Catenella*), sea grasses (*Thalassia hemprichii*, *Enhalus acoroides*, and *Halophila ovalis*), salt marsh (*Spartina*), and other floras such as different epiphytes (Kathiresan 2010). In the tropical mangrove forests, there are approximately 100 epiphytic species from the Orchidaceae, Bromeliaceae, Cactaceae, Araceae, Piperaceae, and Polypodiaceae families scattered through the canopy and on the trunks of mangrove trees.

Mangrove-associated faunal species are zooplankton (the genera *Acartia*, *Acrocalanus*, *Macrosetella*, *Euterpina*, *Oithona*), sponges (Biemna *caribbean*, *Haliclona cuaçaoensis*, *Haliclona implexiformis*), ascidians (*Ecteinascidia turbinata*), epibenthos (*Vallentinia gabriellae*), infauna (*Notomastus lobatus*, *Halmyrapseudes spaansi*), meiofauna (*Parapinnanema ritae*, *P. alii*, *P. rhipsoides*), prawns (*Alpheus euphrosyne*, *A. microrhynchus*), shrimp (*Penaeus vannamei* and *P. monodon*), crabs (*Scylla serrata*, *Clibanarius laevimanus*), insects (*Mesovelia pol-*

hemusi, *Telmapsylla*, *Nasutitermes nigriceps*, *Apis dorsata*), mollusks (*Littoraria fasciata*, *Cerithidea mazatlanica*), fish (*Rivulus marmoratus*, *Cyprinodon*, *Centropomus undecimalis*), amphibians (*Rana*, *Bufo*, *Microhyla*, *Rhacophorus*), reptiles (*Crocodylus porosus*, *Varanus bengalensis*, *V. salvator* and *V. flavescens*, *Ophiophagus hannah*, *Vipera trimeresurus*), birds (*Ajala ajala*, *Cosmorodium albus*, *Eudocimus ruber*, *Pandion haliaetus*, *Sterna hirundo*, *Dendrocygna arborea*), and mammals (*Platanista gangetica*, *Macaca mulatta*, *Lutra perspicillata*, *Pteropus conspicillatus*, *Pteropus alecto*, *Cebus paella paella*, *Rhinoceros sondaicus*, *Bubalus bubalis*, *Cervus duvauceli*, *Axis porcinus*) (Kathiresan and Bingham 2001; Giri et al., 2011).

13.4 Medicinal Potential of Various Mangrove Plants

Mangroves represent a unique ecosystem with vast biological resources and immeasurable medicinal potential waiting to be revealed (Thatoi et al. 2016a, b). Now, how far they intend to venture into the enormous possibilities of never-ending medicinal potential of these mangrove plant species is a question for those intelligent and native thinkers. In this century, the time has already taken a turn and the race has already begun. Therefore, the sooner the search is made the better is the possibility of finding something that might forever shift the paradigm to the next level of human welfare. Presently, many of the biomedical potentials from mangrove plant species are slowly and steadily uncovered by creative thinkers from different corners of the world. Some of these medicinal prospectives include antibacterial, antifungal, antiviral, antidiabetic, and anti-inflammatory activities (Boopathy and Kathiresan 2010; Kathiresan 2010; Patra et al. 2011; Chakraborty and Raola 2016). An overview of such activities has been presented in this section with a special emphasis on the anticancer prospective.

13.4.1 Anticancer Potential of Mangrove Plants

Natural products of mangrove origin have long been investigated for their potential benefits since the folk era. By consistent transformation of trails and selection, mankind has learnt the significance of these plant juices and crude extracts as therapeutics for the treatment of various human disorders and aliments. During the 1900s, most medicines were obtained through cooking, infusion, or maceration of roots, barks, leaves, or flowers (Reddy and Grace 2016a). Currently, these natural products are considered to play a substantial role in the development of new drugs and therapeutics but are confined to traditional practices and uses. A database named Traditional Chinese Medicine contains 21,334 compounds derived from 2402 plants, of which about 5278 compounds have anticancer activity against highly potent cell lines. Moreover, the anatomization manifested that about 75% of these

5278 compounds are highly similar to either preclinical, clinical, and/or approved stages of anticancer drugs (Kathiresan and Manivannan 2008; Dai et al. 2016). Despite the irreplaceable and momentous potential of these bioactive phytocompounds, they are not exploited up to their maximum potential, and there is hardly any authenticate record/list/database on anticancer compounds from mangrove origin.

The search for anticancer compounds from mangrove plants is supposed to be an extensive research of the present curio, but the eye-catching results of the classical, chemically derived therapeutic agents have somewhat blinded the renewability of present research. Despite the seemingly irreversible side effects, chemical theranostics against cancer has considerably increased during recent times in comparison to natural therapeutic agents. Among all possible natural therapeutics, the use of mangrove species is least explored, although they possesses comparatively higher contents of heterogeneous bioactive compounds which is a unique characteristic of mangrove species (Boopathy and Kathiresan 2010; Debbab et al. 2010; Valli et al. 2012). However, with the advancement of technology and growing concern of side effects from drugs of chemical origin, a search for novel metabolites from terrestrial and especially mangroves has gained a considerable attention in recent times. In specific, an apprehension to cancer bioactive compounds contained in the *plant extract of Acanthus ilicifolius was shown to be effective in* preventing DNA alterations and significantly inhibited the proliferation of ascites tumor in animals and certainly improved the survival rate (Chakraborty et al. 2007). Likewise, Khajure and Rathod (2011) evaluated the cytotoxic potential of the ethanolic acetate extract of the same plant against KB and HeLa cell lines by comet assay. They found the results very promising with an increased inhibition of cancer cells. Later, Patil et al. (2011) also studied the cytotoxic activity but of a different plant species, *Excoecaria agallocha*. They evaluated the cytotoxicity of the ethanolic extract of stems against cancerous cell lines, namely, Capan-1 and Miapaca-2, and found the IC_{50} values of 4 μg/ ml and 7 μg/ml, respectively. A study by Uddin et al. (2012) isolated seven phytocompounds, namely, tetracosane, patriscabratine, quercetin3-O-β-d-glucosyl-(6→1)-α-l-rhamnoside, quercetin-3-O-β-d-glucoside, quercetin-3-O-α-lrhamnosyl-7-O-β-d-glucoside, quercetin-3-O-α-l-rhamnopyranoside, and kaempferol from the methanolic extract of the aerial parts of *Acrostichum aureum*, a mangrove fern. Further, cytotoxicity study using FITC Annexin V apoptosis assay revealed that these biocompounds possess potential to induce toxicity through apoptosis and necrosis against AGS gastric cancer cell lines. Thus, their research highlighted the possible use of this plant as a source of biocompounds and proved its traditional usage in treating peptic ulcer. Satapathy et al.(2013) screened various bioactive compounds and evaluated the antitumor activity of different parts of few mangrove plants, namely, *Phoenix paludosa* (leaf), *Avicennia alba* (leaf), *Heritiera fomes* (stem, leaf), *E. agallocha* (stem, bark, leaf), *Sonneratia apetala* (bark), and *Suaeda maritima* (stem, leaf) from Bhitarkanika natural reserve of Odisha, India. In another study by Smitha et al. (2014), the ethyl acetate extract of a mangrove plant *Acanthus ilicifolius* leaves and roots showed a significant cytotoxicity against two cancer cell lines MCF-7 and PA-1. Both leaf and root extracts recorded the highest inhibition of

MCF-7 and PA-1 cells at the concentration of 100 μg/mL. Likewise, Neumann et al. (2015) have reported that dolabrane-type of diterpenes tagalsins isolated from a mangrove suppressed tumor growths by reactive oxygen species-mediated apoptosis and cell cycle arrest. More recently, arbutin derivatives of *Heliciopsis lobata* plant showed a moderate cytotoxic effect on MGC-803 cells (Wei-Yan et al. 2016). Some of the mangrove plants with bioactive phytocompounds possessing anticancer activity and their structures are presented in Tables 13.1 and 13.2.

Table 13.1 Bioactive compounds isolated from mangrove plants with anticancer activities

Name of plant	Compound isolated	Activity against cell lines	References
Avicennia marina	Stenocarpoquinone B	K562 and HeLa cell lines	Han et al. (2007)
Xylocarpus granatum	Catechin, epicatechin	–	Das et al. (2014)
Cucumaria frondosa	Frondoside A	Urothelial carcinoma cells	Dyshlovoy et al. (2017)
A. germinans	3-chlorodeoxylapachol	K662 and HeLa cells	Mahmud et al. (2014)
	Xylomexicanin	Human breast carcinoma and KT cells	
	Gedunin	CaCo-2 colon cancer cell line	
Xylocarpus granatum	Photogedunin		
Sonneratia ovata	Sonnercerebroside, dehydroconiferyl alcohol, methoxydehydroconiferyl alcohol	AChE inhibition and cytotoxicity against HeLa, NCI-H460, MCF-7 cell lines, and PHF cells	Nguyen et al. (2015)
Soneratiia apetala	Mitomycin C	Cancer and diabetes	Patra et al. (2014)
Bruguiera gymnorrhiza	–	HepG2 cell line	Reddy and Grace (2016a)
Aegiceras corniculatum			
Aegialitis rotundifolia			
Lumnitzera racemosa			
A. marina	–	MCF-7 cell line	Reddy and Grace (2016b)
A. officinalis			
Calophyllum inophyllum			
B. gymnorrhiza			
A. corniculatum			
Phoenix paludosa	–	High toxicity against MCF-7, MDA-MB-231, SK-BR-3, and ACHN cell lines	Samarakoon et al. (2016a)
		Less cytotoxic against normal cell lines HEK-293, MCF-10A	

(continued)

Table 13.1 (continued)

Name of plant	Compound isolated	Activity against cell lines	References
Aegiceras corniculatum	–	MCF-7, and HepG2 cell lines	Samarakoon et al. (2016b)
Avicennia officinalis			
Bruguiera gymnorrhiza			
Excoecaria indica			
Heritiera littoralis			
Lumnitzera littorea			
L. racemosa			
Nypa fruticans			
Pemphis acidula			
Phoenix paludosa			
Rhizophora apiculata			
R. mucronata			
Scyphiphora			
Hydrophyllacea			
Sonneratia alba			
S. caseolaris			
Acanthus ilicifolius	Methylapigenin 7-o-β-D-glucuronate-flavone glycosides	MCF-7 and PA-1 cell lines	Singh and Aeri (2013), Smitha et al. (2014)
Catharanthus roseus	Vincristine, vinblastine	Hodgkin's disease, choriocarcinoma cells	Sain and Sharma (2013)
Acrostichum aureum	Tetracosane	HT9 colon cancer, estrogen-dependent breast cancer (MDA-MB-231) cells, and gastric cancer cells	Uddin et al. (2011)
	Quercetin-3-*O*-βd-glucoside,quercetin-3-O-βd-glucosyl-(6 → 1)-α-l-rhamnoside, quercetin-3-*O*-α-l-rhamnoside, quercetin-3-*O*-αl-rhamnosyl-7-O-β-$_d$-glucoside (2S,3S)-sulfated Pterosin C	Moderately cytotoxic against AGS, MDA-MB-231, and MCF-7 cells	Uddin et al. (2012)
	Kaempfero, patriscabratine	Gastric cancer (AGS) cells	Uddin et al. (2013)
Heliciopsis lobata	6-[(E)-2methoxy 5cinnamoyl] arbutin1, 2-[(E)-25dihydroxy-cinnamoyl] arbutin2	Cancer and MGC-803 cells	Wei-Yan et al. (2016)

(continued)

Table 13.1 (continued)

Name of plant	Compound isolated	Activity against cell lines	References
X. granatum	Xylogranatins A, B, C, D	–	Yin et al. (2006)
	Granaxylocarpins A, B	P-388 leukemia cells	Yin et al. (2007)
Ceriops tagal	Tagalsins B, C, D, E, F, G, H, W, 9, 10	Hematologic cancer (human T-cell leukemia), HCT-8, Bel-7402, BGC-823, A549, and A2780 cell lines	Yang et al. (2015)
X. granatum	Xylogranatumine A–F	A549 tumor cell	Zhou et al. (2014)

Table 13.2 Some anticancer compounds isolated from selected mangrove plants

Plants	Isolated compounds	References
Cerbera odollam	2′-o-acetyl cerleaside A, 17b-neriifolin, cerberin	Chan et al. (2016)
Xylocarpus granatum	Photogedunin, catechin, epicatechin, procyanidins	Das et al. (2014)
Cucumaria frondosa	Frondoside A	Dyshlovoy et al. (2017)
Avicennia marina	Stenocarpoquinone B	Han et al. (2007)
Sonneratia ovata	Sonnercerebroside, (7S,8R) dehydroconiferyl alcohol	Nguyen et al. (2015)
Avicennia germinans	3-chlorodeoxylapacho, xylomexicanin, gedunin	Mahmud et al. (2014)
Acrostichum aureum	Quercetin-3-O-αl-rhamnosyl-7-O-β-d-glucoside, Tetracosane, Quercetin-3-*O*-βd-glucoside, Quercetin-3-*O*-β-d-glucosyl-(6 → 1)-α-l-rhamnoside, Quercetin-3-*O*-α-l-rhamnoside, kaempferol	Uddin et al. (2012)
Heliciopsis lobata	6′-[(E)-2″, methoxy, 5″ cinnamoyl] arbutin 1, 2′-[(E)-2″, 5″ dihydroxy-cinnamoyl] arbutin 2	Wei-Yan et al. (2016)
Ceriops tagal	Tagalsins A, B, C, D, E, F, G, and H, tagalsins W, tagalsins 9 and 10	Yang et al. (2015)
Xylocarpus granatum	Xylogranatins A, B, C, D	Yin et al. (2006)
Xylocarpus granatum	Granaxylocarpins A, B	Yin et al. (2007)
Xylocarpus granatum	Xylogranatumine A–F	Zhou et al. (2014)

13.4.1.1 Endophytes from Mangrove Plants and Their Anticancer Activity

Endophytes, mostly fungi, actinomycetes, and bacteria, are organisms that live in harmony within the intercellular spaces of plant tissue with no apparent damage to their host. In another way, it can be said that they live in a symbiotic relationship with their host plants. They epitomize a vast variety of microbial adaptations that have been developed in the special or remote environment. Plant-host interaction requires persistent and extended reactions against the defense mechanisms of the host by the endophyte (Ariole and Akinduyite 2016). The secondary metabolites produced by microorganisms in general and endophytic microorganisms in specific have been investigated and explored for various industrial purposes including pharmacological and clinical applications including anticancer therapeutics. An introduction to some of these endophytes and their anticancer activities are described below.

Streptocarbazoles A and B, two novel indolocarbazoles with an unknown feature of cyclic N-glycosidic linkages between 1,3-carbon atoms of the glycosyl moiety and two indole nitrogen atoms of the indolocarbazole core, were isolated from the marine-derived actinomycetes strain *Streptomyces* spp. which is sometimes also found in endophytic form in mangrove plants. Fu et al. (2012) found that streptocarbazole A possesses cytotoxicity against HL-60 and A-549 cell lines and could arrest the cell cycle of HeLa cells at the G2/M phase. Divergolide D, isolated from *Streptomyces* spp. HKI0576 associated with *Bruguiera gymnorrhiza*, a mangrove plant from China, was found to exhibit a significant antitumor activity against pancreatic cancer PANC-1, lung cancer LXFA 629 L, sarcoma SAOS-2, and renal cancer RXK 486 L cell lines (Xu et al. 2014). Lam et al. (2014) isolated 52 endophytic actinomycetes from 3 different species of mangrove trees, namely, *Sonneratia caseolaris*, *S. paracaseolaris*, and *Lumnitzera racemosa*, in Nam Dinh Province, Vietnam. Among them, only two strains (2E20 and 2E29) showed both antifungal and root growth inhibition activities and exhibited anticancer activity against cancer cell lines KB, SK-LU-1, HepG2, and MCF7. Wang et al. (2012) reported the cytotoxic effect of polyphenols obtained from *Penicillium expansum* 091006 associated with *Excoecaria agallocha*, a mangrove plant. Endophytic bacteria also contribute to several physiological beneficial functions of the host plants such as plant growth promotion and increased resistance against pathogens and parasites. In general, endophytic bacteria include both Gram-positive and Gram-negative bacteria that have been isolated from different plant species (Arunachalam and Gayathri 2010). There are a number of endophytic bacteria such as *Bacillus* sp., *Staphylococcus* sp., *Sporosarcina* sp., *Pseudomonas* sp., *Serratia* sp., *Stenotrophomonas*, *Micromonospora* sp., and many others that contain diverse bioactive compounds with pharmaceutical significance (Eldeen and Effendy 2013). Several sesquiterpenoids were isolated from the mangrove origin fungus, *Diaporthe* sp. (Zang et al. 2012).

SZ-685C is a natural, biologically active substance isolated from the secondary metabolites of the mangrove endophytic fungus, *Halorosellinia* spp., collected from

the South China Sea. It is an anthraquinone and has a high potency against six different cancer cell lines derived from human breast cancer (Xie et al. 2010; Hasan et al. 2015). Cultivation of *Acremonium* sp., a fungal isolate, produced two novel hydroquinone derivatives, namely, 7-isopropenyl bicyclo[4.2.0]octa-1, 3, 5-triene-2, 5-diol-5-β-d-glucopyranoside and 7-isopropenyl bicyclo[4.2.0]octa-1,3,5-triene-2, 5-diol (Abdel-Lateff et al. 2002). An endophyte (*Talaromyces flavus*) from the mangrove plant *Sonneratia apetala* contained cytotoxic norsesquiterpene peroxides (Li et al. 2011). *Penicillium chrysogenum* isolated from the mangrove plant *Acanthus ilicifolius* contained new chitin analogues A–C (1–3) and one new xanthone derivative. The penicitol A–C and penixan acid A were reported to show anticancer activity against HeLa, BEL-7402, HEK-293, HCT-116, and A549 cell lines (Wenqiang et al. 2015). Likewise, *Sonneratia ovata* Backer (Sonneratiaceae) is another widely distributed plant species in the mangrove forests of Cambodia, Vietnam, Thailand, and Indonesia. From these plant leaves, Nguyen et al. (2015) structurally elucidated the following chemical compounds such as sonnerphenolic A, sonnerphenolic B, and sonnerphenolic C, sonnercerebroside (cerebroside), lignans, steroids, triterpenoids, gallic acid derivatives, phenolic derivatives, and 1-O-benzyl-β-d-glucopyranose. Some of these isolated compounds inhibited acetylcholinesterase (AChE) activity and exhibited activity against NCI-H460 (human lung cancer), HeLa (human epithelial carcinoma), PHF (primary human fibroblast), and MCF-7 (human breast cancer) cell lines at 100 μg/mL concentration. *Pseudolagarobasidium acaciicola* isolated from *Bruguiera gymnorrhiza*, another mangrove plant, also contained 20 unknown compounds and 2 known metabolites (Merulin A and Merulin D). The compound terpene endoperoxide exhibited greater anticancer activity against the promyelocytic leukemia cell line, HL-60 (Wibowo et al. 2016). *Pestalotiopsis microspora* is another mangrove-derived endophytic fungus which contains 7 new 14-membered macrolides, pestalotioprolides C, D–H and 7-O-methylnigrosporolide, together with four known analogues, pestalotioprolide B, seiricuprolide, nigrosporolide, and 4,7-dihydroxy-13-tetradeca-2,5,8-trienolide. Some of these metabolites have shown anticancer property against murine lymphoma cell line and human ovarian cancer cell line, A2780 (Liu et al. 2016). *Streptomyces cheonanensis* VUK-A is also a mangrove-derived fungal endophyte and contains two metabolites, namely, 2-methyl butyl propyl phthalate and diethyl phthalate, the former showed cytotoxicity against MDA-MB-231, OAW-42, HeLa, and MCF-7 cell lines (Mangamuri et al. 2016). *Pestalotiopsis neglecta* (endophyte), isolated from the mangrove species *Cupressus torulosa*, was reported to possess cytotoxic activity against human embryonic kidney (HEK) cell lines (Sharma et al. 2016). Further, GC-MS analysis of the methanol extract of the species revealed the presence of different cytotoxic and antiproliferative compounds such as nonadecane and 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6- methyl, which paves the way for future use as anticancer agents.

13.4.1.2 Anticancer Potential of Other Sources Found in Mangrove Ecosystem

Non-endophytic bacteria, fungi, actinomycetes, and algae found in the mangrove ecosystem produce various secondary metabolites and can be a great source of anticancer drugs. Some studies have been documented with the prevention of carcinogenesis by the potent chemicals produced from the marine flora. However, secondary metabolite of marine flora for the treatment of cancer is still not fully utilized in comparison to terrestrial habitats. Many researches have been carried out on marine flora, and their novel chemicals have shown their potentiality to be employed in finding drugs with greater efficacy for the treatment of cancer. Some of these chemical compounds are depicted in Table 13.3.

13.4.1.2.1 Bacteria

Bacterial population in the fertile mangrove water is higher than fungi. Marine bacteria produce secondary metabolites such as antibiotics (e.g., marinone), enzymes (arylsulphatase, L-glutaminase, chitinase, L-asparaginase, cellulase, protease, phosphatase), and some of the novel anticancer compounds such as bryostatins and discodermolide (Manivasagan et al. 2014).

13.4.1.2.2 Actinomycetes

Streptomyces, *Micromonospora*, *Jishengella*, and *Salinispora* are important genera of actinomycetes found in mangrove ecosystems. Indole and alkaloids including indolosesquiterpenes, indolocarbazoles, macrolides, and benzene derivatives are the main natural products of the genus *Streptomyces*. They all have been proven to be valuable sources of potentially useful bioactive metabolites for the treatment of cancer (Fu et al. 2012; Yuan et al. 2013; Dong et al. 2014; Tan et al. 2015).

13.4.1.2.3 Fungi

Mangrove consists of endophytic fungi *Halorosellinia* sp., *Guignardia* sp., and *Phomopsis* sp. and produces potent chemical derivatives which have been investigated for anticancer activity (Chen et al. 2009; Tao et al. 2010; Thatoi et al. 2013) and antifungal activities (Huang et al. 2008; Thatoi et al. 2013). Likewise, the chemicals produced by mangrove foliar fungi have been also been studied extensively for their potentiality to be utilized as anticancer drugs.

Table 13.3 Some of the marine floral derivatives and their anticancer activities

Marine flora	Chemical compounds	Biological activity	References
Actinomycetes			
Streptomyces spp.	Indolocarbazoles, streptocarbazoles A and B	Antitumor activity	Fu et al. (2012)
Streptomyces spp.	7 azlomycin F analogues, macrocyclic lactones	Antibiotic, anticancer	Yuan et al. (2013)
Streptomyces spp.	Pyrrolopyrazine, carboline and dicarboxylic acid ester	Anticancer activity	Tan et al. (2015)
Fungal flora			
Hypocrea lixii, *Irpex hydnoides*	Crude extract	Anticancer activity and cytotoxic effect	Bhimb et al. (2011)
Pestalotiopsis microspora	Crude extract	Antimicrobial and anticancer activity	Joel and Bhimba (2012)
Algal			
Stylopodium sp.	Stypoldione	Cytotoxic	Gerwick and Fenical (1981)
Cystophora sp.	Meroterpenes, usneoidone	Antitumor	Urones et al. (1992) and Boopathy and Kathiresan (2010)
Nostoc linckia, *N. spongiaeforme*	Borophycin	Cytotoxicity against human epidermoid carcinoma (LoVo) and human colorectal adenocarcinoma activity	Banker and Carmeli (1998) and Vijayakumar and Menakha (2015)
Nostoc sp.	Cyptophycin 1	Cytotoxicity against human tumor cell lines and human solid tumors	Moore (1996) and Boopathy and Kathiresan (2010)
Lyngbya boulloni	Apratoxin A	Cytotoxicity to adenocarcinoma	Luesch et al. (2001)
Stigonema sp.	Scytonemin	Antiproliferative	Stevenson et al. (2002)
Leptolyngbya sp.	Coibamide A	Cytotoxicity effect against adenocarcinoma and NCIH460 lung and mouse neuro-2a cells	Medina et al. (2008)

13.4.1.2.4 Algae Growing in Mangrove

Mangrove algae are the highest contributor among the marine flora to produce anticancer compounds. Cyanobacteria produce many bioactive compounds (toxins) which can be applied in pharmaceuticals (Jha and Zi-Rong 2004; Thajuddin 2005; Uddin et al. 2011). Scytonemin, apratoxin, cryptophycin, stypoldione, coibamide A, largazole, fucoidan, etc. are produced by mangrove algae which have been investigated for their anticancer activity.

13.4.2 Other Potential Activities of the Mangrove Species

13.4.2.1 Antibacterial Activity

Different research studies on mangrove plants have highlighted their use as an important source of antimicrobial drugs. *Suaeda maritima* is a mangrove species widely distributed on the landward margin of mangrove ecosystem across different ranges and has been reported to exhibit antimicrobial property against several pathogenic microbial strains, namely, *Shigella flexneri*, *Bacillus brevis*, *B. subtilis*, *B. licheniformis*, *Pseudomonas aeruginosa*, *Vibrio cholerae*, and *Streptococcus aureus* (Patra et al. 2011). *Peltophorum pterocarpum* is another native mangrove species of Sri Lanka, the Andaman's, the Malay Bawong, and Malaysia whose leaves extract contains different phytochemicals and possess potent antimicrobial activity against *P. aeruginosa, S. aureus, B. cereus, Escherichia coli, Klebsiella pneumonia, Salmonella typhi, Serratia marsecens, Acinetobacter baumannii, Enterobacter* sp., *Proteus mirabilis,* and *Enterococcus* sp., (Sukumaran et al. 2011). Likewise, Saad et al. (2011) reported the antimicrobial properties of *Lumnitzera littorea* against various pathogenic microbes. *Avicennia officinalis*, a species of mangrove plants occurring at Parangipettai, Chidambaram district, also showed antimicrobial activity against the pathogenic bacterium, *B. megaterium* (Valentin et al. 2012). *Lumnitzera littorea* is another mangrove plant distributed widely in the east coast of Africa, Southeast Asia, and Australia and is known to possess antimicrobial potential against certain pathogenic bacteria like *B. cereus*, *P. aeruginosa*, and *Cryptococcus neoformans* (Saad et al. 2011). *Sonneratia apetala*, a mangrove plant extensively found in the Bhitarkanika Sanctuary along the Odisha Coastline, also possessed antibacterial activity against infectious bacteria such as *S. aureus*, *S. flexneri*, *B. licheniformi*, *B. brevis*, *Vibrio cholera*, *P. aeruginosa*, *S. epidermidis*, *B. subtilis*, and *E. coli* (Patra et al. 2014).

13.4.2.2 Antifungal Activity

Rhizophora mangle L. (*Rhizophoraceae*), a red mangrove plant widely distributed along the tropical and subtropical coasts of America from Bermuda to Florida, Occidental Africa, and the islands of Fiji, Tonga, and New Caledonia of the lower swampy zones, possesses significant antifungal properties. In traditional medicine, *Rhizophora mangle* has been used as an antifungal and antiulcer agent (Berenguer et al. 2006). The bark extract of this species had antifungal activity against a pathogenic fungus *Fusarium oxysporum* (Simlai and Roy 2013). *A. schaueriana* extensively distributed throughout the Brazilian Atlantic Forest possesses secondary metabolites such as lapachol, α-lapachone, naphtho [2,3-*b*] furan-4,9-dione, 2-isopropyl, and avicenol-C which have been evaluated and found to be active against another fungus, *Colletotrichum gloeosporioides* (Fardin et al. 2015).

13.4.2.3 Antiviral Activity

Natural herbs are one of the ancient sources for antiviral substances. The antiviral substances extracted from mangrove plants show high efficacy, low toxicity, and minor side effects. *Peltophorum pterocarpum* is a native mangrove species of Sri Lanka, the Andaman, and the Malay Bawong, Malaysia. The bark of this species contains various phytochemicals that are effective against many disease-causing viruses (Sukumaran et al. 2011). *Excoecaria agallocha* distributed across the coast regions of South China contains polyphenolic compounds, namely, excoecariphenols A–D (1–4), known to have anti-hepatitis C virus (HCV) activity (Jia et al. 2009). Similarly, the compound 2″-(methoxycarbonyl)-5″- methylpentyl 2′-methylhexyl phthalate (a novel phthalic acid ester) isolated from *A. aureum* aerial parts growing in the Bangladesh mangrove region exhibited in vitro antiviral activity against human parainfluenza virus, dengue virus, and chikungunya (Uddin et al. 2013). The mangrove plant, *Xylocarpus moluccensis*, found in the Tang forests of China contains eight new khayanolides, named as thaixylomolins G–N (1–8), and two new phragmalins (9 and 10). These compounds have a strong inhibitory potential against disease-causing virus, influenza A (Li et al. 2015). *Ceriops tagal*, another mangrove species spread along the costal belt of Africa, the South Pacific islands, and South Asia including China possessing bioactive compounds belonging to different chemical classes (alkaloids, flavonoids, and polyphenols), has been proved to be effective against white spot syndrome virus (WSSV) (Sudheer et al. 2012). Likewise, *Aegiceras corniculatum* found near Xiamen City of Fujian Province possesses four compounds and is observed to be active against HCV protease and SecA and ATPase as well as VSVG/HIV-luc pseudotyping virus (Xu et al. 2014).

13.4.2.4 Antidiabetic Activity

Several mangrove plant species have been discovered with antidiabetic properties including *Ceriops decandra* which is a traditional folk remedy for diseases like angina, diabetes, diarrhea, dysentery, hematuria, and hemorrhage. The plant extract from *C. decandra* has high potential against diabetes mellitus (Alikunhi et al. 2010). Three mangrove plants of *Rhizophora* species (*R. apiculata*, *R. mucronate*, and *R. annamalayana*) contain insulin-like antigen and exhibit antidiabetic potential against alloxan-induced diabetic in animal model (Alikunhi et al. 2011). *Nypa fruticans* Wurmb. (Arecaceae) is well-known for its traditional uses by the local practitioners against different ailments in southern regions of Bangladesh. Studies had revealed that *N. fruticans* extract possesses antihyperglycemic potential in glucose loaded in an animal model (Reza et al. 2011). *Pongamia pinnata* (L), *P. glabra* Vent., and *Millettia pinnata* (L) are widely distributed throughout the mangrove areas in the southern part of Thailand and contain pyranoflavonoids useful in the treatment of diabetes (Anusri et al. 2014).

13.4.2.5 Anti-inflammatory Activity

Certain mangrove plants have also been found to contain phytocompounds with anti-inflammatory activity. The methanolic extract of *Rhizophora apiculata*, a common mangrove plant found in Asia and Africa, when evaluated for its anti-inflammatory and antitumor activity against B16F10 melanoma cells in BALB/c, mice showed high anti-inflammatory activity (Prabhu and Guruvayoorappan 2012). Likewise *Acanthus ilicifolius* (Acanthaceae), a local inhabitant of the Sundarbans, India, is used to treat a variety of diseases. The methanolic extract of *Acanthus ilicifolius* leaves (MEAL) possesses significant anti-inflammatory properties against gastric ulcer and duck hepatitis B (Mani et al. 2012; Wei et al. 2015). The bark extracts of *Rhizophora mangle* contain various polyphenolic compounds, including tannins and other metabolites (e.g., epigallocatechin-3-gallate, procyanidins), which have anti-inflammatory effects against gastric ulcer (De-Faria et al. 2012). *Rhizophora mucronata* is a true mangrove plant extensively distributed along the coastal region of India and is rich in terpenoids with a strong potential against inflammation (Chakraborty and Raola 2016).

13.4.2.6 Antioxidant Activity

Streptomyces lincolnensis M-20 cell extract was proven to contain an antioxidant agent, protocatechualdehyde (Kim et al. 2008). This compound exhibited a potent antioxidant activity by scavenging the free radicals 2,2-diphenyl-1-picrylhydrazyl (DPPH). In another study, Ser et al. (2015) isolated a new *Streptomyces* strain MUSC 149 T from the soil of mangrove forest located in Tanjung Lumpur, Peninsular Malaysia. *Streptomyces* MUSC 149 T-cell extract showed a dose-respondent DPPH free radical scavenging activity. The lowest activity (1.1 ± 1.4%) was found when 0.125 mg/ml of cell extract was used, while the highest activity (36.5 ± 3.0%) was observed with the use of 2.0 mg/ml. Further, chemical analysis of the extract revealed the occurrence of antioxidant agent(s) in the cell extract. The identified compounds included hexadecane, butanoic acid, 2-methyl-,benzoic acid, 3-methyl- (3R,8aS)-3-methyl-1,2,3,4,6,7,8,8a-octahydropyrrolo[1,2-a]pyrazine-1,4-dione, and Pyrrolo[1,2-a]pyrazine-1,4-dione,hexahydro.

13.5 Conclusion and Future Prospects

The past information on various uses of plants, microbes, and any other biological or chemical substances is the basis for the current practice of novel drug discovery. However, it is often the future that ignites and sets forth the path of the present advancements which leaves behind an illustrious past and a momentous future. The illusion of nanotechnology changes and revolutionizes the course of medicinal sciences, and drug discovery is based on the scientific exploration of a noble smart

seminatural therapeutic for the treatment of diseases like cancer. It is not that the current anticancer theranostic phytocompounds are incompetent in achieving the present appreciable goal, but rather the target unspecific delivery and low availability and dispersity are some of the huddles that need much attention. The remedy for these problems could be brought about by the application of nanotechnology. A wide range of nanocarriers are being used for the treatments of various types of cancer such as phytosynthesized silver and zinc nanoparticles by using *Heritiera fomes* and *Sonneratia apetala* mangrove plant aqueous extracts as a reducing agents. These biosynthesized nanoparticles also possessed strong pharmacological activities including antioxidant, antidiabetic, anti-inflammatory, and antimicrobial potentials. Thus, these nanoparticles could be very useful for various biomedical applications. The use of synthetic therapeutics with anticancer activity can alternatively replaced by the use of natural bioactive compounds conjugated to nanocarriers, which is both effective and show negligible side effects. In the coming decade advanced medication can be formulated using phytocompounds of mangrove origin as nanotherapeutics against cancer. Likewise, there are polymeric and other inorganic nanocarriers that have the capacity to carry anticancer phytocompounds of mangrove origin, but still the research is limited. Thus, various neglected species of mangroves can be a new source of natural compounds which could be successfully used for treating numerous human ailments. However, more emphasis should be given to explore these natural sources for the discovery of novel therapeutics against cancer. Despite the awareness, if still the diversifying serviceability of mangrove species is not put to their explicit use, then the incomprehensible credibility of their anticancer activity would continue to rest in its own shadow for ages.

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