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Review Article

PHARMACOLOGICAL PROFILE OF MANGROVE ENDOPHYTES - A REVIEW

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ABSTRACT

Natural products play a key role in meeting the global demand for new pharmacologically active substances. Since marine and coastal environments possess considerable biological diversity having added reasons to produce secondary metabolites, they are looked upon as potential candidates for drug discovery. Mangroves inhabit the transition zone between land and sea; therefore it is assumed that they would produce outstanding natural products on their own. The unique environment of mangrove forests harbors diverse groups of microorganisms, including the endophytes. Endophytes, which live asymptomatically within living plant tissues, are an under explored group of microorganisms and hence studies on these microbes from unique ecosystems offer resources with immense biotechnological potential. This article attempts to give an insightful review on the efforts currently being made to explore the bioactive compounds produced by mangrove endophytes.

Keywords: Endophyte, Mangrove, Secondary metabolite, Bioactive compound.

INTRODUCTION

Natural products, generally secondary metabolites produced by living organisms, present an alternative route to address the ever increasing need for new drugs, because of their low production costs, novelty and structural diversity. Plants and microbes have been viewed as the most promising sources of natural products. Ethnobotanical knowledge has given an adequate basis for further investigation of medicinal properties in traditionally used plants. After the discovery of penicillin, research has been augmented to explore new microbial metabolites with a broad spectrum of applications in medicine, industry and agriculture. With advances in instrumentation, the list of natural products having therapeutic value has increased and a plethora of new compounds are continually being isolated [1]. This constitutes almost 50% of the new drugs introduced to the market from 1981 to 2010, and approximately 75% of anti-infective agents are natural products or natural product derivatives [2].

However, commercial success of plant natural products requires a large quantity of plant material to produce sufficient amount of the drug. This has raised concerns like environmental degradation, loss of biodiversity and threat to endangered species. It is in this scenario that the isolation of taxol producing endophyte *Taxomyces andreanae* has provided an alternative approach to obtain a cheaper and more available product *via* microorganism fermentation [3]. Earlier, the bark of the tree *Taxus brevifolia* [4] was being sourced for the commercial production of taxol. The rationale that traditional medicinal plants can be used as the starting point to investigate endophytes for the production of biologically active compounds is further supported by examples like the endophytic fungus *Entrophospora sp*. producing the cytotoxic plant alkaloid Camptothecin [5] and production of podophyllotoxin from the fungus *Trametes hirsuta* [6]. The knowledge that microorganisms residing inside the plant tissues may produce similar, if not, the same bioactive compounds as that produced by their plant hosts, is of great research interest from a commercial point of view. It is relatively easier to scale up the fermentation process of microbes, thus enabling large scale production of biologically active compounds to meet industrial demands [1].

Endophytes

Bacon and White (2000) [7], gave an inclusive and widely accepted definition of endophytes as "microbes that colonize living, internal tissues of plants without causing any immediate, overt negative effects". It is believed that in many cases, these microbes function as biological defense for the plant against foreign phytopathogens. The protection mechanism of the endophytes is exerted directly by releasing metabolites to attack any antagonists, or indirectly by inducing host defense mechanisms[1]. Endophytes can also promote plant growth through different mechanisms like production of phytohormones[8], synthesis of siderophores[9], nitrogen fixation, solubilisation of minerals[10], ethylene suppression[11] or via assisting phytoremediation [12]. Endophytes can be transmitted from one generation to the next through the tissue of the host, seed or vegetative propagules[13].

Among the 300 thousand known higher plant species, each plant is host to one or more endophytes [14]. It has been suggested that interactions between endophytes and their respective plant host contribute to the co-production of bioactive molecules [15]. But interactions between host plant and endophyte are still far from being understood. Moreover, the symbiotic nature of this relationship indicates that endophytic bioactive compounds are likely to possess reduced cell toxicity, as these chemicals do not kill the eukaryotic host system [1]. Therefore, it is hypothesized that endophytes could be useful sources of lead compounds in drug discovery.

The rationale for selecting promising plant sources, proposed by Strobel et al. (2004) [14] gives particular interest on plants which themselves are used as medicinal plants and plants that populate distinct biotopes and have to cope with extreme living conditions like cold, heat or multitudinous competing organisms in their natural environment; for example, inhabitants of rainforests or mangrove forests. Ultimately, biological diversity implies chemical diversity; due to the constant chemical innovation that exists in ecosystems where the evolutionary race to survive is the most active [16]. Hence the chance to find novel compounds with high bioactivities is most probable in these ecosystems.

Mangroves and their endophytes

Mangroves are intertidal forest wetlands established at the interface between land and sea in tropical and sub tropical latitudes [17]. Mangrove forests protect coastlines from wave action and prevent coastal erosion. They also reduce damages in inland areas during storms. They are well adapted to their extreme environmental conditions of high salinity, changes in sea level, high temperatures and anaerobic soils, through pneumatophoric roots, stilt roots, salt-excreting leaves, and viviparous water dispersed propagules. Mangroves also offer the most productive and biologically complex ecosystems. Numerous mangrove plants have been used in folklore medicine. Despite the fact that intensive research on mangrove metabolites has sprung up only in the last two decades, there have been

several publications in recent years that tend to establish that they can be a source of novel compounds along with providing a new source for many already known biologically active compounds [18, 19].

Due to the presence of a rich source of nutrients, mangroves are referred to as the homeland of microbes [20]. Although the mangrove ecosystem is rich in microbial diversity, only less than 5% of the species present have been described [21]. Several studies have been conducted on the endophyte communities of mangrove plants found along the coastlines of the Indian, Pacific and Atlantic oceans[22]. The endophyte assemblage has been found to vary with different plant parts (leaves, twigs, roots), age of the host plant and changes in season [23]. Moreover, since mangrove forests are an open interface ecosystem connecting upland terrestrial and coastal estuarine ecosystems, the endophytes in mangroves constitute a consortium of soil, marine and freshwater microbes [24]. Thus they represent an interesting source of new lead structures for medical applications. This review describes endophytes from mangroves and their diverse compounds with bioactivities reported in the past decade. It also highlights the traditional medicinal uses and recent investigations on bioactivities of common mangroves, in the hope that this would assist in narrowing down the most suitable source material for isolation of endophytes.

Bioactive compounds from mangroves

The common chemical constituents present in the mangroves are aliphatic alcohols and acids, amino acids, alkaloids, carbohydrates, carotenoids, hydrocarbons, free fatty acids including polyunsaturated fatty acids, lipids, pheromones, phorbol esters, phenolics and related compounds, steroids, triterpenes and their glycosides, tannins and other terpenes[25]. Even though several chemical studies have been conducted on mangrove plants, reports pertaining to their activity-structure relationship are very few. Some common mangroves found in tropical and sub tropical regions, their traditional uses, general chemical constituents, *in virto* bioactivity etc are given in Table 1.

Table 1: Common mangroves with *in vitro* bioactivity

Mangrove	Traditional uses	General Chemical composition	*In vitro* activity
Acanthus ilicifolius	to treat paralysis, asthma, diuretic, dyspepsia, hepatitis, leprosy, rheumatic pains. analgesic, anti-inflammatory, leishmanicidal [18,26]	benzoxazoline, long chain alcohols, triterpenes, steroids, triterpenoidal saponins alkaloid, acanthicifolin [18,27]	central nervous system depressant, antipyretic, hypnotic, muscle relaxant, anti fungal[28] anticancer [29,30] anti-viral [18] antioxidant [31,32] anti-inflammatory [32] antinociceptive [33] anti ulcer [34]
Aegiceras corniculatum	cure for asthma, diabetes, rheumatism. fish poison [18]	benzoquinones, carotenoids, tannins, coumarins, flavonoids, minerals; polyphenols, proteins, sugars, saponins, triterpenes [18]	antifunagal,piscicidal [18] anti-inflammatory[3, 35] antioxidant [31,35] hepatoprotective [35] antinociceptive [36] antidiabetic [37]
Avicennia marina	cure for skin diseases [38]	terpenoids, steroids naphthalene derivatives, flavones, glucosides[39]	cytotoxic[40-42] antibacterial [40,41,43] antifungal [44] antioxidant [45,46]
Avicennia officinalis	aphrodisiac, diuretic,cure for hepatitis,leprosy, [18]	arsenic,alkaloids, saponins, tannins, triterpenoids [47, 48]	antibacterial [43]
Bruguiera sexangula	cure for sore eyes, shingles and burns.[49]	phenolics, steroids, alkaloids, tannins [50]	antibacterial [43]
Ceriops decandra	astringent, anti hemorrhage, to treat pain, ulcers, hepatitis [26,51]	lipids,sterols triterpines [52]	anti nociceptive [51] anti bacterial [53,54] antioxidant [31,55] anti inflammatory [55] anti fungal [28] anti diabetic [56]
Derris trifoliata	stimulant, spasmodic, counter irritant, laxative, fish poison, pesticide [18]	saponins,alkaloids, carbohydrates, flavonoids,steroids, triterpenes, [18]	piscicidal,insecticidal [57]
Excoecaria agallocha	uterotonic, fish poison, dart poison, treatment of epilepsy,conjunctivitis, dermatitis,hematuria, leprosy,toothache [18,26]	phorbol ester, flavanone, glycoside, various di- and triterpenoids, dichloromethane, lignin, pentosan, α-cellulose saponin,tannins,phenols,volatile oils [58-68] [69]	anti bacterial [43,69,70] anti nociceptive, gastro protective [71] neuropharmacological effect, anti microbial and cytotoxic [72,73] antioxidant [74-76] anti allergic [76] anti hyperglycemic [77] anti fungal [28] anti-HIV[78,79] metabolic depression of the rice field crab [80] biocidal effects on marine organisms and phytoplankton, piscicidal [81]
Heritiera littoralis	mosquito control,cure for diarrhea, fish toxicant	sesquiterpenes, triterpene ester, cinnamoylglyco- flavonoid, tribuloside,	insecticidal, anti mycobacterial, antioxidant, anti fungal [27,82,83]

	[18]	flavonoid glycosides, pentacyclic triterpenoids [18,82]	
Kandelia candel	cure for diabetes [84]	alkaloids, tannins, saponins, polyphenols[85]	antioxidant [86,87]
Rhizophora apiculata	astringent, for diarrhoea, nausea, and vomiting,antiseptic, antihaemorragic, cure for typhoid fever [18] treatment of diabetes,	triterpenes, steroids, and a novel triterpenoid ester [18]	anti HIV[78,79] antibacterial [43]
Rhizophora mangle	angina, boils, bruises, fungal infections, diarrhoea,dysentery, elephantiasis,malarial fever, leprosy, plaster for fractured bones, tuberculosis, antiseptic [18]	tannins,phytosterols, saturated and not saturated long chain fatty acids[88]	insecticidal [89] anti diabetic [90] anti ulcer [88] antioxidant [87]
Rhizophora mucronata	treatment of elephantiasis, haematoma, hepatitis, ulcers, as febrifuge [18]	saponin,tannins, flavanoids, phenols,volatile oils, alkaloid rhizophorine [18,69]	anti bacterial [69] anti HIV [78,79] antidiabetic [37,91]
Sarcolobus globosus	relief for rheumatism, dengue fever. [92]	rotenoid, isoflavone, chromone, phenolic glycosides[92,93]	cytotoxic [94,95] thrombolytic [95]
Sonneratia acida	sprain poultices, arresting hemorrhage[18]	phenols,anthraquinones,diterpenoid [18]	anti ulcer [96]
Sonneratia alba	swellings and sprains [18]	saponin,tannins,phenols,volatile oils [69]	anti bacterial [69]
Sonneratia caseolaris	to treat hemorrhages, piles, sprain poultices [18,26]	fatty acids, sterols hydrocarbons, flavonoid, luteolin and its glycosides, oleanolic acid [97-99]	antioxidant [98,100,101] anti diabetic [99,102] anti fungal [28] bactericidal [103] anti nociceptive[101] anti allergic [100]
Thespesia populnea	to treat fever including those caused by malaria [18]	triterpene,lupeol, gossypol, quinines[18]	anti fertility, cytotoxic, anti bacterial, anti steroidogenic [104-106]
Xylocarpus granatum	relief from malaria fever, dysentery, diarrhea,cholera, inflammation,other abdominal problems [26, 94]	limonoids, flavanoids, procyanidins [107]	CNS depressant [108] antioxidant [94,109] anti cancer [110] anti diarrheal [111] anti microbial [53,94,112,113]
Xylocarpus moluccensis	gastro intestinal disorders, malarial fever, astringent, aphrodisiac, elephentiasis,swelling of breast [26,94,114]	flavanoids, procyanidins, limonoid ester, alcohol esters [18,94]	anti diarrheal [115] anti bacterial [94] [115-117] cytotoxic[114,116] CNS depressant [108,118] antioxidant [94]

Pharmaceutical potential of mangrove endophytes

Research has revealed that natural products obtained from endophytic microbes possess anti microbial, anti neoplastic, antioxidant, anti diabetic, immunosuppressive, anti thrombotic, anti-inflammatory and anti Alzheimer's activity among others[119]. Mangrove endophytes have also turned out to be of great potential for the pharmaceutical industry.

Cytotoxic /anti cancer activity

The common drugs for cancer treatment show nonspecific toxicity to proliferating normal cells, possess severe side effects and are not effective against many forms of cancer. Many investigations have revealed mangrove endophytes from different geographic areas with cytotoxic properties. The chemical components responsible for cytotoxic action have been identified in most of the cases (Table 2).

Table 2: Mangrove endophytes with *in vitro* cytotoxic/ anti cancer properties

Endophyte	Mangrove	Geographic area	Bio active compound identified	Ref
Streptomyces sp. (gt-20026114)	*Aegiceras corniculatum*	South china	cyclopentenone derivatives	[120, 121]
Dothiorella sp. HTF3	*Avicennia marina*	Jiulong River estuary, Fujian Province, China	cytosporone B	[122]
Penicillium sp.	*Aegiceras corniculatum*	-	polyketides	[123]
Nigrospora sp.	*Bruguiera sexangula*	Hainan Island, China	anthraquinones	[19]
Bionectria ochroleuca	*Sonneratia caseolaris*	Hainan Island, China	cyclic depsipeptides bionectriamides A-C	[19]
Aspergillus flaviceps	*Acanthus ilicifolius*	-	cytochalasin z17 and rosellichalasin	[124]
Talaromyces sp	*Kandelia candel*	Q'iao Island, Zhuhai, China	7-epiaustdiol, 8-O-methylepiaustdiol stemphyperylenol secalonic acid A	[125]
Paecilomyces sp	unidentified mangrove	Taiwan Strait	paeciloxocins A	[126]
unidentified fungus	*Xylocarpus granatum*	Samutsakorn Province,	merulin A	[127]

XG8D		Thailand	merulin C	
Penicillium sp.	*Acanthus ilicifolius*	South China	penicinoline	[128]
Penicillium expansum	*Excoecaria agallocha*	Wenchang, Hainan, China	expansols A &B	[129]
Fusarium sp.	*Kandelia candel*	-	isoflavone, 5-O-methyl-2′-methoxy-3′-methylalpinumisoflavone	[130]
unidentified endophytic fungus	*Sonneratia apetala*	China	sonnerlactone and its diastereoisomer	[131]
unidentified endophytic fungus	*Avicennia marina*	China	1,7-dihydroxy-2-methoxy-3-(3-methylbut-2-enyl)-9H-xanthen-9-one and 1-hydroxy-4,7-dimethoxy-6(3-oxobutyl)-9H-xanthen-9-one	[132]
Nocardiopsis sp. a00203	*Aegiceras corniculatum*	Jimei, Fujian province, China	norcardiatones(2-pyranone derivatives)	[133]
streptomyces sp.	*Bruguiera gymnorrhiza*	-	xiamycin (pentacyclic indolosesquiterpene)	[134]
Aspergillus ustus	*Acrostichum aureum*	Guangxi Province, China	drimane sesquiterpene	[135]
Talaromyces flavus	*Sonneratia apetala*	South China Sea	talaperoxides (norsesquiterpene peroxides)	[136]
Bionectriao chroleuca	*Sonneratia caseolaris*	-	pullularins E &F	[137]
Fusarium oxysporum	*Rhizophora annamalayana*	Vellar estuary,India	taxol	[138]
Pestalotiopsis microspora VB5	*Rhizophora mucronata* *Avicennia officinalis*	Pichavaram, India	-	[139]
Hypocrea lixii VB1	Rhizophora mucronata Avicennia officialis Avicennia marina	-	-	[140]
Diaporthe sp.		Kampung Pasir		[141]
Eupenicillium sp.	-	Pandak, Sarawak Malaysia	-	
Alternaria sp. R6	*Myoporum bontioides*	-	resveratrodehydes A–C	[142]

Antimicrobial activity

The novel antimicrobial metabolites from endophytes offer an alternative option to overcome the increasing levels of drug resistance by human pathogens and are of great interest to the scientific community, as infectious diseases are one of the leading causes of human mortalities globally [1,143]. Many bioactive compounds of mangrove endophytes have been found to show broad spectrum activities against both fungi and bacteria (Table 3), including methicillin resistant *Staphylococcus aureus* and vancomycin resistant *Enterococcus faecalis* [144].

Antioxidant activity

Antioxidants are commonly found in medicinal plants, vegetables, and fruits. Antioxidants have been considered promising agents for the prevention and treatment of ROS-linked diseases such as cancer, cardiovascular disease, atherosclerosis, hypertension, ischemia/reperfusion injury, diabetes mellitus, neurodegenerative diseases (Alzheimer and Parkinson diseases), rheumatoid arthritis, and aging [158]. Huang and coworkers (2007) [159] suggested that the phenolic contents were the major antioxidant constituents of the endophytes. *Phomopsis amygdale,* an endophytic fungus isolated from the mangrove plant in Karankadu, India, showed potent antioxidant activity against both ABTS and DPPH radicals [160]. Endophytic colonization of *Trichoderma* was found to be higher in mangrove leaves of *Aegiceras corniculatum* than the other mangroves of Andaman and Nicobar Islands and was demonstrated to be with potential for antioxidant activity[161]. Two new resveratrol derivatives, namely, resveratrodehydes A and C, isolated from the endophytic fungus *Alternaria sp*. R6, obtained from the root of *Myoporum bontioides* A. Gray also showed moderate antioxidant activity by DPPH radical scavenging assay [142].

Anti protozoal activity

Four depsipeptides from *Bionectria ochroleuca* obtained from *Sonneratia caseolaris* exhibited anti tryponosomal activity against *Trypanasoma brucei* [19]. Branches and leaves of black, red, and white mangroves around Coquina Beach, Florida and the Everglades showed promising fungal isolates with initial activity against *Plasmodium falciparum* [162]. Endophytes from *Kandelia obovata, Avicennia marina* and *Lumnitzera racemosa of* mangrove areas of Hong Kong and Taiwan were also screened for new antimalarial compounds. A new polyketide Dicerandrol D was isolated from a strain of *Diaporthe sp.* (CY-5188) which showed strong activity against *P. falciparum* with low cytotoxicity [163].

Anti viral activity

Two of the anthraquinones obtained from *Nigrospora sp*. isolated from *Bruguiera sexangula* exhibited good prophylactic effects against human rhinoviruses [19]. Altenusin obtained from *Alternaria sp*., isolated from *Sonneratia alba* also showed prophylactic effects against infection by selected human rhino viruses[19]. Xiamycin A obtained from *Streptomyces sp* strain GT 2002/1503 an endophyte from *Bruguiera gymnorrhiza* exhibited selective anti-HIV activity [134]. Two isoindolones from a fungal endophyte *Emericella sp*. (HK-ZJ), isolated from the inner bark of *Aegiceras corniculatum* demonstrated anti viral activity against influenza A virus (H1N1) [164].

Alpha glucosidase inhibitory activity

Alpha glucosidase inhibitors can retard the uptake of dietary carbohydrates and suppress post prandial hyperglycemia and could be useful for treating diabetic and/or obese patients [165]. Two new compounds 6′-O-desmethylterphenyllin, 3-hydroxy-6′-O-desmethylterphenyllin, and the known 3,3″-dihydroxy-6′-O-desmethylterphenyllin obtained from the endophytic fungus *Penicillium chermesinum*, isolated from *Kandelia candel* collected at South China Sea in Guangdong Province, China, exhibited strong inhibition of α-glucosidase showing significantly higher effects than the positive control genistein [166].

Compound 07H239- isolated from the endophytic mangrove fungus *Xylaria* sp. BL321 showed inhibitory activity on *α*- glucosidase with an increase in concentration [167]. New vermistatin derivatives, 6 demethylpenisimplicissin and 2''-epihydroxydihydrovermistatin which were isolated from the mangrove endophytic fungus *Penicillium sp.* HN29-3B1 from *Cerbera manghas*, also exhibited α-glucosidase inhibitory activity [168].

Table 3: Mangrove endophytes with *in vitro* antimicrobial activity

Endophyte	Mangrove	Geographic area	Bio active compound identified	*In vitro* activity	Ref
*Streptomyces sp. (*gt-20026114)	*Aegiceras corniculatum*	South China	cyclopentenone derivatives	anti bacterial	[120,121]
Dothiorella sp. HTF3	*Avicennia marina*	Jiulong River estuary Fujian Province, China	cytosporone B	anti fungal	[122]
Cumulospora marina	*Acanthus ilicifolius*	southwest coast of India	-	anti bacterial	[145]
*Aspergillus sp*2	*Acrostichum aureum*			anti bacterial	
*Aspergillus sp*3				anti bacterial	
Pestalotiopsis sp				anti fungal	
Cladosporium sphaerospermum	*Aegiceras corniculatum*	Hainan Island, China	citrinin	anti bacterial	[19]
Fusarium incarnatum	*Pluchea indica*	Hainan Island, China	equisetin	anti bacterial	[19]
Nigrospora sp	*Bruguiera sexangula*	Hainan Island, China	anthraquinones	anti bacterial	[19]
Alternaria sp	*Sonneratia alba*	Hainan Island, China	altenusin	anti bacterial	[19]
Alternaria sp	*Sonneratia alba*	Hainan Island, China.	xanalteric acids I&II	anti bacterial	[146]
Talaromyces sp	*Kandelia candel*	Qiao Island, Zhuha China	7-epiaustdiol stemphyperylenol secalonic acid A	anti bacterial	[125]
Paecilomyces sp.,	an unidentified mangrove	Taiwan Strait	paeciloxocins A(depsidone-type metabolite)	anti fungal	[126]
Nocardiopsis sp A00203	*Aegiceras corniculatum*	Jimei, Fujian province, China	2-pyranone derivatives (norcardiatones)	anti bacterialanti fungal	[133]
endophytic bacteria	*Rhizophora apiculata, Avicennia marina, Excoecaria agallocha Ceriops decandra Aegiceras corniculatum*	Pichavaram India	-	anti bacterial, anti fungal	[147]
Penicillium sp., Aspergillus sp. Acremonium sp. Fusarium sp, Ampelomyces sp.	*Rhizophora mucronata*	Porong river estuary Indonesia	-	anti bacterial	[148]
Streptomyces sp HKI0595	*Kandelia candel*	-	xiamycinB xiamycin A (indolosesquiterpe-nes)	anti bacterial	[144]
Aspergillus niger, *Curvularia pallescens Guignardia bidwelii Paecilomyces variotii Mycelia Sterilia*	*Laguncularia racemosa*	Brazil	-	anti bacterial	[149]
Pestalotiopsis sp. PSUMA69	*Rhizophora apiculata*	Sutun province, Thailand	butenolide, (pestalolide) diphenyl ethers(pestalotethers A-B) pestheic acid chloroisosulochrin dehydrate chloroisosulochrin	anti fungal	[150]
Pestalotiopsis microspora VB5	*Rhizophora mucronata Avicennia officinalis*	Pichavaram India	-	anti bacterial	[139]
Hypocrea lixii VB1	Rhizophora mucronata, Avicennia officinalis Avicennia marina	-	-	anti bacterial	[140]
fungusBUEN 880	*Thespesia populnea*	eastern part of Thailand	-	anti fungal	[151]
Penicillium chrysogenum, MTCC 5108	*Porteresia coarctata*	Chorao Island, Mandovi estuary,Goa	C19H21O2N3 (indole & di ketopiperazine moiety)	anti bacterial	[152]
endophytic bacteria	-	Pichavaram,India	-	anti bacterial	[153]
Guignardia sp. Neosartoya sp.	-	Kampung Pasir Pandak,	-	anti bacterialanti	[141]

		Sarawk, Malaysia		fungal	
Aphyllophorales sp. (JQ34006)	*Bruguiera cylindrica*	-	-	anti bacterial	[154]
Serratia sp *Bacillus* *Pseudomonas Micrococcus* *Enterobacter*	*Rhizophora mucronata*	-	-	anti bacterial anti fungal	[155]
Fusarium sp *Penicillium* sp *Alternaria* sp., *Nigrospora* sp., *Rhizopus* sp	*Rhizophora annamalayana*	Vellar estuary, southeast coast of India	5-eicosene and 1dodecanol, 2-methyl	anti bacterial	[156]
Endohytic bacteria	*Avicennia alba* *Avicennia marina Bruguiera gymnorrhiza*	Bali and Manado, North Sulawesi, Indonesia	-	anti bacterialanti fungal	[157]

Anti Acetylcholinesterase activity

Acetylcholinesterase (AChE) inhibitors are currently an approved therapy for the treatment of Alzheimer's disease(AD). Nevertheless, the search for potent and long acting AChE inhibitors that exert minimal side effects in AD patients is still ongoing [169]. Sporothrin A isolated from the mangrove endophytic fungus *Sporothrix sp*.(#4335) showed strong inhibition of acetylcholinesterase[170]. Two known terphenyls isolated from mangrove endophytic fungus *Penicillium chermesinum* (ZH4-E2) also showed inhibitory activity towards acetylcholinesterase.[166]. Other potential AChE inhibitors from mangrove endophytes include arigsugacin I, a new α-pyrone meroterpene and two known compounds, arigsugacin F and territrem B, isolated from *Penicillium sp*. sk5GW1L of *Kandelia candel* [171] and two polyketides from Penicillium *sp*. sk14JW2P [172].

Anti inflammatory activity

Non steroidal anti inflammatory compounds are of high significance in treating inflammatory diseases. Extracts of *Irpex hydnoides, Aspergillus flavus, Schizophyllum commune, Neurospora crassa, Hypocrea lixii, Pestalotiopsis microspora, Aspergillus oryzae* and *Meyerozyma guilliermondi* isolated from mangroves showed anti-inflammatory activity. Their activities were comparable to that of standard drug Indomethacin [173].

Anti mycobacterial activity

Tuberculosis is becoming a major health hazard due to multidrug resistant forms of bacilli and new drug sources like natural products are being sought in this regard. *Fusarium sp*. DZ-27 isolated from the bark of *Kandelia Candel* (L)Druce, collected from Dongzhai mangrove forest. Hainan, China yielded fusaric acid. Anti mycobacterial assays showed that fusaric acid and its cadmium and copper complexes possess potent inhibitory activities against *Mycobacterium bovis* BCG strain and *M. tuberculosis* H37Rv strain [174].

Effect on angiogenesis

Angiogenesis is a vital process in many areas of tissue maintenance and regeneration [175], while angiogenesis inhibitors are cancer fighting agents. Endophytic fungus *Phomopsis sp*., isolated from the stem of *Excoecaria agallocha* collected in Dongzhai, Hainan, China yielded Phomopsis-H76 A, B and C. Compounds B and C were found to possess a unique pyrano[4,3-b] pyran-5(2H)-one ring system unprecedented in nature. Compound A induced formation of ectopic vessels in the subintestinal vessel plexus (SIV), in zebra fish embryos whereas compound C inhibited blood vessel formation [176].

L- calcium channel inhibition activity

Calcium channel blockers relax and widen blood vessels making it easier for blood to flow through the vessels. thus lowering blood pressure. Calcium channel blockers are also frequently used to alter heart rate, to prevent cerebral vasospasm, and to reduce chest pain caused by angina pectoris [177]. Almost all of them preferentially or exclusively block the L-type voltage gated calcium channel [178]. Xyloketal F, an unusual metabolite with strong L-calcium channel blocking activity, was isolated from the mangrove endophytic fungus Xylaria sp. (#2508) collected at the South China Sea coast [179].

CONCLUSION

The pharmacological potential of the marine habitats of Indian coast line including mangrove forests still remains largely unexplored. Marine natural product bioprospecting has yielded a number of drug candidates in recent years. Endophtyic microbes are also now being recognized as a new and poorly explored source of bioactive compounds. This review shows that many endophytes inhabiting the diverse mangrove forests of the world, importantly fungi, have proved themselves to be rich sources of new bioactive metabolites.

Despite their ecological and economic importance, many mangrove forests are on the verge of extinction worldwide, basically because of the invasion of aquaculture, agriculture and urban land use. The pharmacological significance of mangrove endophytes can bring about awareness and enthusiasm among the public to safeguard and restore mangroves in critical areas, as they offer an alternative approach in natural product drug discovery without destroying the endangered plants. Substantial progress has been achieved in identifying the mangrove endophytes and their bioactive compounds. More endeavours are expected to bring out their further clinical applications.

CONFLICT OF INTERESTS

Declared None

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