Antimicrobial agents from mangrove plants and their endophytes

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The mangrove designates a inter-tidal wetland ecosystem formed by a very special association of animals and plants in the coastal areas and river estuaries. Mangroves are highly productive ecosystem with various important economic and environmental functions. As mangroves exist under stressful conditions, they have had to develop an extraordinary array of defenses (chemicals), for protection and adaptation with the requirement of such challenging condition.

Endophytes, mostly fungi, bacteria and actinomycetes are organisms that live in the intercellular spaces of plant tissue with no apparent damage to their host. They represent a huge diversity of microbial adaptations that have developed in special sequestered environment. Plant host interaction requires sustained and prolonged reactions against the defense mechanisms of the host by the endophyte. This could act as a selection pressure for the development of novel metabolic pathways. The secondary metabolites produced by microorganisms in general and endophytic microorganisms specifically, have been investigated and explored for various industerial purposes including pharmacological and clinical applications. A number of drugs were developed from metabolic agents produced by these microorganisms such as ß-lactam antibiotics, griseofulvin and cyclosporine. Bacteriocins are peptides produced by prokaryotes during the various stages of bacterial growth. These products are associated with antimicrobial effects such as bacteriocidal or bacteriostatic agents against microganisms related to the producer strain. Bcateriocins have been explored for their potential utility in human and animal health application. Example is nisin, a widely characterized bacteriocin produced from the lactic acid bacterium *Lactococcus lactis* and has been accepted by WHO as a food biopreservative. Since a number of bacterial species belonging to different genera such as *Bacillus*, *Pseudomonas*, *Serratia*, *Stenotrophomonas* and *Micromonospora* among others are reported found in different plant parts as endophytes, it is possible to assume that mangrove bacterial endophytes may have a great chance of secretion of valuble competitive bioactive substances like bacteriocins due to their special environment and complicated growth conditions.

Endophytes in general are viewed as an outstanding source of bioactive natural products that need to be further investigated. This chapter highlights the importance of some mangrove and mangrove associated plants and their endophytes as a source of promising antimicrobial agents.

Keywords Mangroves, Endophytes, Bacteriocins, Natural products

1. Introduction

The collective noun mangrove designates a inter-tidal wetland ecosystem formed by a very special association of animals and plants in the coastal areas and river estuaries throughout the low lying tropical and sub-tropical latitudes [1].

The term mangrove is also used to designate halophytic and salt resistant marine tidal forests consist of trees, shrubs, palms, epiphytes, ground ferns and grasses. These elements are associated in stands or groves [2]. It is an ecological assemblage rather than a taxonomic or morphological grouping. Mangroves are usually found in tropical climates due to their special requirements of consistent warm conditions for development and survival. They are highly productive ecosystem with various important economic and environmental functions [1]. Mangroves include diversified habitats such as core forests, litter forest floors, mudflats, and adjacent coral reefs and sea grass ecosystems, the contiguous water bodies consist of the rivers, bays, inter tidal creeks, channels and backwaters. Mangroves can exist under wide ranges of salinities, tidal amplitudes, winds, and temperatures, muddy and anaerobic soil conditions. This variable habitat conditions make them very rich in biodiversity. Mangroves are still play an important role to many people who live along tropical shorelines. They have been managed in some countries as a sustained yield forest crop. Recently their ecological, environmental and socio-economic importances have also been emphasized [3].

As mentioned earlier, Mangroves exist under stressful conditions such as violent environments, high concentration of moisture, high and low tides of water, and abundant living microorganisms and insects. Due to this special growth environment, mangroves produce diverse group of metabolic substances with wide range of biological activities such as antiviral, antibacterial, antifungal and insecticidal. To date, only about 200 bioactive metabolites have been recorded from the mangroves of tropical and sub-tropical populations [1].

Large number of mangrove plant species have been used in traditional medicine. Different extracts from mangroves and mangrove associated species were shown to demonstrate diverse effects against human, animal and plant pathogens. However, very limited investigations have been carried out to identify the metabolite agents that possible to be responsible for their bioactivities. The medicinal properties of mangrove and mangrove associated plants represent a wide domain for several biological applications that need to be explored.

Endophytes is a term used broadly to describe variable life strategies of the symbiosis ranging from facultative saprobic, parasitic, exploitive, mutualistic and commensalistic symbioses. Some authors use the term to indicate a suite of microorganisms that grow intra-and/or intercelullarly in the tissues of higher plants without causing over symptoms on the plants in which they live in [4]. In this chapter, we followed a definition describing the term as: microorganisms including bacteria and fungi that can be detected at a particular moment within the tissues of apparently healthy plant host [5]. Endophytes have proven to be rich sources of bioactive natural products. The endophytes may provide protection and improvement of survival conditions to their host plant by producing a plethora of substances. These substances may also have potential bases for various industrial applications based on their interesting chemical structures and characteristics [6]. Recently, some research groups have focused on determination and evaluation of the potentiality of these microorganisms on the production of bioactive compounds. However, still more efforts and work need to be carried out on this field.

Endophytes provide a broad variety of bioactive secondary metabolites with unique structure, including alkaloids, benzopyranones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, and others [7]. These metabolites could be utilized as agrochemicals, antibiotics, immunosuppressants, antiparasitics, antioxidants, and anticancer agents [8].

Endophytic fungi have been isolated and successfully cultured from several terrestrial plants and have also been isolated from lichens. Some of these endophytes produce bioactive substances that are products of the host-microbial interactions [6].

Plant host interaction requires sustained and prolonged reactions against the defense mechanisms of the host by the endophyte. This could therefore, act as a selection pressure for the development of novel metabolic pathways. This situation makes them an exciting field of study in the search for new bioactive substances. The practical example of such products is the taxol, an anti-cancer compound produced in plant *Taxus brevifolia* by the terrestrial endophytic fungus *Taxomyces andreana* [9].

The mangrove habit has proved to be a rich source of endophytes. They occupy the upper part of the trees as the bases of mangrove trunks and aerating roots are permanently or intermittently submerged. Interactions of endophytes under this environmental condition may lead to production of wide group of chemicals of interesting pharmaceutical applications [9]. Antimicrobial metabolites from endophytes may be a promising alternative to overcome the increasing levels of drug resistance by plant and human pathogens due to the fact that endophytes represent a huge diversity of microbial adaptations that have developed in special sequestered and competitive environment. Endophytes therefore, are viewed as an outstanding source of bioactive natural products that need to be fully discovered [10].

2. Antimicrobial properties of some mangrove and mangrove associated plants

Recent studies on biological properties of mangroves have strongly recommended that mangroves should be studied as a valuable source for chemical constituents with potential medicinal and agricultural values [11].

Although the chemical constituents of most mangrove plants still have not been studied extensively, investigations have led so far to the discovery of several novel compounds with prospective medicinal value for the development of new chemotherapeutic agents.

Avicennia marina (Forssk.) Vierh. (Avicenniaceae) has received some attention in determining its important chemical constituents. Some chemical compounds have been isolated and characterized from the plant including: a napthoforan compound with phytoalexin activity, fatty acids [12,11], sterols and hydrocarbons. This study was carried out on the chemotaxonomic significance of eleven mangrove species including *A. marina* [13]. Khafagi et al. [14], evaluated antibacteriophage, antibacterial and anticandidal activities of extracts prepared from roots, cotyledons, leaves and stems of *Avicennia marina*. The authors findings indicated that aqueous extracts of both shoots and roots of the seedlings demonstrated antibacteriophage activity using coliphage against *Escherichia coli* NRRL B-3704.This might indicate an antiviral activity. These findings were later supported by the report of Beula et al. [15], who stated that among the investigated four mangrove plants, *Avicennia marina* leaf extract showed the best antiviral activities. The authors recommended that, the leaf extract of *Avicennia marina* could be subjected to further studies to determine its potential bioprospecting as antiviral agents.

Other researchers have also confirmed the presence of diverse array of bioactive chemical agents during chemical investigations of different parts (barks, leaves, twigs, etc.) of *A. marina* and its endophytes. It was reported that about 123 compounds were isolated from the different parts of the plants [16]. These diverse groups of chemicals including terpenoids and steroids, naphthalene derivatives, flavones, glucosides, phenylpropanoid glycosides, flavonoids, abietane and diterpenoid were reported to possess different biological activities including antimicrobials [16].

Another promising antibacterial activities were also observed with ethyl acetate extract of *Avicennia marina* leaves [17,18] and methanol extract of *Excoecaria agallocha* leaves and shoots [19] beside antifungal activity of methanol extract of *Exoecaria agallocha* and *Bruguiera gymnorrhiza* trunks [20,21]. Ethanol and methanol extracts of leaves and barks of *Bruguiera gymnorrhiza* also showed antibacterial effects against both Gram-positive and Gram-negative bacterial strains used in the assay [21].

Novel inhibitors of HIV-1 reverse transcriptase have also been characterized from the Malaysian tree *Calophyllum inophyllum*. A triterpenoidal saponin isolated from *Acanthus illicifolius* and a novel alkaloid isolated from *Atriplex vesicaria* have revealed antileukemic activity. An investigation of the antibacterial properties of *Rhizophora mucronata* revealed that the active agents were possible to be a mixture of squalene, n-hexadecanoic acid, cyclohexane, phytol and oleic acid. Hu and Wu [22], reported the isolation and identification of eight unique phragmalin ortho esters and thirteen limonoids with new carbon skeleton beside new protolimonoid, protoxylogranatin B (1), from the mangrove plant *Xylocarpus granatum*. Moreover, Li et al.[23], have reported the isolation of eighteen limonoids including ten new structures, named godavarins A–J from the seed of *Xylocarpus moluccensis*. The new isolates were appeared to be including three mexicanolide derivatives. This in addition to the 42 mexicanolides and 23 phragmalins that previously isolated from the wood, seeds, and fruits of *X. granatum* and *X. moluccensis* [24]. Limonoids are important constituents that reported presence mainly in the grapefruit and other citrus. Research on health benefits suggests that citrus limonoids may act as anti-cancer, cholesterol lowering, anti-HIV and anti-feedant compounds. However, Vikram et al. [25], evaluated some limonoids for their potential to antagonize cell-to-cell communication, biofilm formation and expression of Enterohemorrhagic *Escherichia coli* (EHEC) type three secretion system (TTSS). These results suggested that, certain limonoids are inhibitory to the cell-to-cell communication, biofilm formation and EHEC TTSS. Specifically, obacunone demonstrated strong inhibition of EHEC biofilm formation and TTSS. Furthermore, obacunone and other limonoids seemed to inhibit the biofilm formation and TTSS in quorum sensing dependent fashion. These findings indicated that some limonoids may possibly help in antagonizing the EHEC infection process, and may serve as lead compound in development of new antimicrobial molecules [25].

Extracts of *Pemphis acidula* and *Ceriops tagal* were possessed promising antibacterial activities against five selected fish and shrimp pathogens including *Aeromonas hydrophila*, *Vibrio harveyi*, *V.alginolyticus*, *V.vulnificus* and *V.parahaemolyticus*. Methanolic bark extracts of *Cerios tagal* showed higher antibacterial activity against *V.alginolyticus*.This activity was reported to be on a par with the antibiotic drug Streptomycin [26].

Chudhuri and Cuha [27], investigated the role of secondary metabolites agents from some mangrove plants against virulent plant pathogen *Fusarium oxysporum*. Their results indicated that among the thirteen plant studiesd, twelve showed antifungal properties against *F.oxysporum*. The highest activity was recorded for leave extracts followed by bark, roots and fruits. They concluded that *Ceriops decandra*, *Heritiera fomes*, *Nypa fruticans*, *Bruguiera gymnorrhiza, Aegiceras corniculatum* and *Phoenix paludosa* were of high potentiality to be utilized for a biocontrol against *F. oxysporum*.

A report on antimicrobial properties of *Sesuvium portulacastrum* revealed that fatty acid methyl esters (FAME) extracts obtained from the plant showed interesting antibacterial and antifungal activities against some human pathogenic fungal and bacterial strains. Gas chromatographic analysis of FAME confirm the presence of palmitic acid with high concentration followed by oleic acid, linolenic acid, linoleic acid, myristic acid and behenic acid. These chemical constituents may be responsible for the reported antimicrobial activities.

A methanolic leaf and stem extracts from *Dolichandrone spathacea* was evaluated by Saiful et al. [28], against six strains of local MRSA clinical isolates and one ATCC MRSA reference strain. The stem extract possessed high activity compared with the leave extract. Results of phytochemical screening showed the presence of triterpene and saponin which might be responsible for the observed activities [28]. Antimicrobial properties of the *D.spathacea* was also previously reported by Rasadah and Houghton [29].

Sittiwet et al. [30],studied antimicrobial activity of aqueous extract of *Pluchea indica* using pathogenic strains of both Gram-positive and Gram-negative bacteria. Results obtained from the study indicated the antimicrobial effects of the extracts and therefore support the traditional utilization of the plant for urinary tract infection.

Antifungal activity of methanolic, ethanolic and boiling water extracts of *Barringtonia racemosa* leaves were studied and reported by Hussin et al. [31], against *Fusarium* sp., *Tricoderma koningii* and *Penicillium* sp.. The authors stated that best inhibitory effects were observed with the methanolic extracts in all aerial parts of *B.racemosa* . HPLC analysis of the extract of *B. racemosa* (leaves, sticks and barks) confirmed the presence of two different phenolic acids (gallic acid and ferrulic acid) and four different flavonoids (naringin, rutin, luteolin and kaempferol). The results of present study provide scientific basis for the use of the plant as a source of antimicrobial agents.

3. Antimicrobial properties of mangroves endophytes

Molecules derived from natural products have proven to be an excellent source of novel chemical compounds which can be used for the development of new pharmaceutical product and other applications. Mangrove endophytes, have been recognized as rich sources of natural products with unique structures and desirable bioactive properties of secondary metabolites [32,8]. Most of the natural products discovered from endophytes are antimicrobials, anticancers antidiabetes and other bioactive agents with different functional roles [33].

3.1. Antimicrobial properties of fungal endophytes isolated from some of mangrove plants

Fungal endophytes are among the most important groups of eukaryotic organisms that are being explored for clinical applications [8]. Bhimba et al. [9], reported the isolation of foliar fungi from *Rhizophora mucronata, Avicenna officialis* and *A. marina*. Ethyl acetate extract of the metabolic agents produced by the isolated fungi showed high antibacterial activities against human pathogenic strains. The authors concluded that the fungal endophytes revealed their potential to yield potent bioactive compounds for drug discovery programmes.

Christophersen et al. [34], reported isolation and investigation of antimicrobial activities of 227 marine isolated fungi from different sources including mangroves. Different levels of activities were recorded for the tested fungi against the pathogenic bacteria *Staphylococcus aureus* and *Vibrio parahaemolyticus*. Similar findings were also reported by Maria et al. [35], who studied potential antimicrobial properties of 14 endophytic fungi isolated from *Acanthus ilicifolius* and *Acrostichum aureum* against bacteria *Bacillus subtilis, Enterococcus* sp., *Klebsiella pneumoniae, Pseudomonas aerugionsa, Salmonella typhi* and *Staphylococcus aureus* and fungi *Candida albicans* and *Trichophyton metagrophytes*. The authors stated that the tested fungi exhibited antibacterial effects against all bacterial strains tested. During an investigation of the distribution of endophytic fungi in the leaves of mangrove forest trees growing at three different locations in Thailand, Chaeprasert et al. [36], reported that the common fungal endophytes genera isolated were *Cladosporium*, *Colletotrichum*, *Phomopsis* and *Xylaria*. Antimicrobial properties of the isolated endophytic fungi was determined against *Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli* and *Staphylococcus aureus*. The ethyl acetate extracts obtained from the isolated fungi showed inhibitory effects against all the tested bacterial strains. The fungi *Aspergillus* sp also showed inhibitory effects against *Candida albicans.* However, no activity was recorded against *Trichophyton mentagrophytes*. Achemical investigation of extract from the endophytic fungus *Bionectria ochroleuca*, isolated from the inner leaf tissues of the mangrove plant *Sonneratia caseolaris* led to the isolation of two new peptides, pullularins E and F together with three known compounds verticillin D, pullularin C and pullularin A [37]. Peptides are group of compounds consisting of two or more amino acids linked by peptide bond. They are abundantly present in living organisms. Antimicrobial peptides are becoming more popular as better substitutes to antibiotics. They are proven to be effective antimicrobial agents against several bacteria, fungi, viruses and protozoa [38]. Huang et al. [39], reported the isolation, structural elucidation and biological activities of three new metabolites, phomopsin A , B and C , and two known compounds cytosporone B and C from the mangrove endophytic fungus, *Phomopsis* sp. which was isolated from the stem of the mangrove tree *Excoecaria agallocha*. The isolated cytosporone B and C showed antifungal activities against two fungi *Candida albicans* and *Fusarium oxysporum* . Several reports highlighted isolation of different classes of chemcial constituents from fungi and endophytic fungi as part of the secondary metabolites products. These chemicals including: steroids, triterpenoids, tetrahydrosorbicillinol, bisorbibutenolide, agistatine B, parvisporicin, dihydrosporothriolide, pseudocitreoindole, stilbene, kojic acid, acetyl-kojic acid, p-hydroxybenzoic acid ,emodine, chloroemodine, and ergosterol-peroxide, hydroxy-phenylethyl alcohol, nicotinic acid, galacitol, naphthoquinone, phenylacetamide and many more [40,41,42,36,43]. A number of these isolates were proven to be of antimicrobials effects with different level of activities and mechanism of actions [44, 43,36].

3.2. Antimicrobial properties of bacterial endophytes isolated from some of mangrove plants

Endophytic bacteria are ubiquitous in most plant species with no indication of harmful effects on the hosts. They can be isolated from surface of plant tissue or extracted from within the plant. They are believed to be originated from the epiphytic bacterial communities of the rhizosphere and phylloplane, as well as from endophyte-infested seeds or planting materials [45]. Endophytic bacteria were shown to have several beneficial effects on host plants including plant growth promotion and increased resistance against plant pathogens and parasites. In general, endophytic bacteria including both Gram- positive and Gram- negative bacteria have been isolated from different plant species[46].

Ravikumar et al. [47], demonstrated *in vitro* antibacterial activity of endophytic bacteria isolated from halophytic plants. Of the total isolated starins, at least, 2 strains showed broad-spectrum of antibacterial activity against shrimp pathogens. The strains were identified as *Bacillus thuringiensis* and *Bacillus pumilus*. Another study on bioprospecting potential of endophytic bacteria from mangrove plants also indicated the presence of antimicrobial properties of the isolated bacterial endophytes . Of the 28 isolates, 20 strains showed broad spectrum activity, while 5 strains were found active against Gram-positive bacteria and fungi and 7 strains were active against Gram-negative bacteria [33]. No available reports describing isolation of antimicrobial agents from mangrove endophytic bacteria when compared with reports on endophytic fungi. However, on a relevant topic, Lee et al.[48], reported the isolation of three compounds from Gram-negative, nonobligate predator bacterial strain 679-2 which exhibits broad-spectrum antimicrobial activity. The isolated agents wer identified to be pyrrolnitrin, maculosin, and a new compound which was named banegasine. Both maculosin and banegasine (displayed no antimicrobial activities alone), were found to possess synergetic effects on the antimicrobial activity of pyrrolnitrin.

Microbial antagonism can also lead to the production of valuable secondary metabolites. In particular growth inhibitors, as one of the mechanisms of adaptation, which gives advantage in competition for available nutrients and living space [49]. This is very much true wih the bacterial endophytes regarding their special growth environment.Under such stressful environment, microbes produce an extraordinary array of microbial defence systems including broad spectrum classical antibiotics, metabolic byproducts such as lactic acids, lytic agents and different types of proteins and bacteriocins [50].

Bacteriocins are a heterogeneous group of ribosomally synthesized, cationic, amphiphilic, and/or hydrophobic antimicrobial peptides [51]. Bacteriocins have the ability to inhibit closely related and sometimes more distantly related strains of bacteria and therefore, play a major role in the natural defense systems of several bacterial species [52]. Several reports have discussed the isolation of different endophytic bacterial strains from mangrove plants such as: *Bacillus* sp, *Staphylococcus* sp, *Sporosarcina* sp, *Pseudomonas* sp, *Serratia* sp, *Stenotrophomonas*, *Micromonospora* sp and many more [51,47,33,53]. These strains are known to produce different types of bacteriocins based on their structure, mode of actions and chemical properties [48]. A report on bacteriocin from mangrove environment confirmed the isolation of a bacteriocin named enterocin isolated from *Enterococcus faecium.* The isolate showed antimicrobial effects on *Lactobacillus plantarum*, *Enterococcus facealis*, *Listeria monocytogens* and *Salmonella paratyphi*.

Further efforts by Shin et al.[54], towards characterization of bacteriocins produced by bacteria inhibiting gastrointestinal tract of broiler chickens, had led to the isolation of bacteriocins produced by *Enterococcus faecium* SH 528, *E. faecium* and *Pediococcus pentosaceus* SH 740. These bacteriocins showed inhibitory activity against *Clostridium perfringens* and *Listeria monocytogenes*.

Smitha and Bhat [55], studied antimicrobial properties of *Bacillus licheniformis* against some Gram-positive bacteria. The active constituent seemed to be a bacteriocin like inhibitory substances which was identified as 14 kDa.N-terminal amino acids. It was described as a novel, pH-tolerant and thermostable bacteriocin . Another novel bacteriocin named thuricin 17 was also isolated as a secondary metabolite produced by *Bacillus thuringiensis.* The thuricin 17 reported to have bacteriocidal and bacterioststic effects against some related *Bacillus* sp and also against Gram-negative bacteria *E.coli* [56]. Kayalvizhi and Gunasekaran, [51], isolated and characterized a novel broad-spectrum bacteriocin from *Bacillus licheniformis*. The isolated bacteriocin showed a wide range of inhibitory effects against *Bacillus* sp, *Staphylococcus* sp, *Streptococcus* sp and *Listeria* sp. The genus *Bacillus* is a heterogeneous group of Gram-positive, facultative anaerobic, heterotrophic nitrifiers, denitrifiers, nitrogen fixers, iron precipitators, selenium oxidizers, oxidizers and reducers of manganese, chemolithotrophs, acidophiles, alkalophiles, psychrophiles, thermophiles and others endospore-forming bacteria beside other characteristics enable these bacteria to colonize a wide variety of ecological habitats. The genus was known to produce large number of bacteriocins such as subtilosin produced by *B. amyloliquifaciens*, bacillocin by *B. licheniformis*, cerein by *B. cereus* ,haloduracin by *B. halodurans*, and subtilin by *B. subtilis* and more others. Many of the *Bacillus* bacteriocins belong to the lantibiotics, a modified peptides widely disseminated among different bacterial strains of the genus *Bacillus*. Lantibiotics are among the best-characterized antimicrobial peptides at the levels of peptide structure, genetic determinants and biosynthesis mechanisms [55,57].

Bacteriocins are now being explored for their potential utilization in different applications. Their application to meet numerous human challenges is only limited by our imagination and efforts of creativity [50].

Mangrove environment and endophytic bacterial mangroves are a rich source with diverse inhabitant of microorganism that need be discovered and heavily investigated as an endless source of novel constituents with diverse applications including of course antimicrobial agents.

4. Chemical classes associated with mangrove plants

Several useful metabolites with novel chemical structures belong to diverse chemical classes were isolated from mangrove plants (Table 1). These classes including:

Aalkaloids (usually occur as heterocyclic nitrogenous bases but may sometimes contain sulfur (dithiolanes)). Carbohydrates, lignins and polysaccharides **(**found abundantly in higher terrestrial plants, fungi, and seaweed and consist of compounds such as sugars, starch, and cellulose). Fatty acids (are long chain alkanoic acids and refer principally to straight chain, saturated or unsaturated monocarboxylic acids). Phenolic compounds (include wide range of aromatic compounds with hydroxyl substituents. The calss include polyphenolics, flavonoids phenolic quinones, lignans, xanthones and coumarins among others.). Phytoalexins (a wide range of organic compounds, collectively called phytoalexins, including alcohols, alkaloids, flavonoids, lignans, polyketides, polyacetylenes, quinines). Tannins (tannins are polyphenolic substances widely distributed among higher plants) [1]. Many isolates belonging to these classes were proved to be of interest as traditional and /or industrial pharmacological antimicrobial agents Table 1.

Table 1 Chemical constituents and antimicrobial properties of some mangrove and mangrove associated plants and their endophytes.

Botanical names	*Antimicrobial properties*	*Associated endophytes*	*Bioactive agents from plants and/or endophytes*	*References*
Acanthus ilicifolius	Antibacterial Anti fungal Antiviral	**Fungi** *Cumulospora marina* and *Pestalotiopsis* sp.	Flavonoids, terpenes steroids and triterpenoidal saponins(stigmasterol).	[1,35, 58,59,15]
Aegiceras corniculatum	Antiviral Antifungal	**Fungus** *Cladosporium sphaerospermum* and **bacterium** *Streptomyces* sp	Aminoacids, benzoquinones, carbohydrates, carotenoids, tannins,coumarins,flavonoids, polyphenols, proteins, sugars, saponins, triterpenes, triterpenes glycosides,*p*-a minoacetophenonic acids, citrinin and quinolactacin.	[1,32,60]
Avicennia marina	antiviral antibacterial antifungal	**Fungi** *Xylaria* sp; *Hypocrea lixii* and **bacteria** *Bacillus* sp., *Enterobacter* sp.	Alcohols, amino acids, carbohydrates, fatty acids, hydrocarbons, inorganic salts, minerals, phytoalexins, carboxylic acids, steroids, tannins, triterpenes, vitamins, n-hexadecanoic acid,cyclic peptides:xyloketals, xyloallenolides.	[16,1,53,61]
Barringtonia racemosa	Antifungal	-	Phenolic acids (gallic acid and ferrulic acid) and four different flavonoids (naringin, rutin, luteolin and kaempferol).	[31]
Bruguiera cylindrica	Antiviral	**Endophytic bacteria**	Sulphur containing alkaloids, tannins.	[1,47]
Bruguiera gymnorrhiza	Antibacterial Antifungal	**Fungus** *Nigrospora* sp.	Compounds indole-3-carbaldehyde; anthocyanins, carbohydrates, carotenoids, catechins, condensed and hydrolysable tannins, diterpenes, gibberellins, fatty acids, hydrocarbons, inorganic salts, lipids, flavans and flavan polymers, minerals, phenolic compounds, procyanidins, proteins, steroids, carboxylic acids and triterpenes.	[60,21,1,62,63]
Calophyllum inophyllum	Antifungal Antiviral Antibacterial	**Endophytic fungi**	Flavonoids, inophyllums, lipids, proanthocyanidin, polymers, xanthones, benzopyrans, coumarins, steroids, triterpenes, xanthones.	[1,64]
Carapa moluccensis	Antibacterial	**Endophytic bacteria** (*Bacillus* sp).	Alkaloids, glycosides, flavanoids,tannins, terpenes, and saponins.	[1,65,66]
Ceriops decandra	Antiviral Antifungal	-	Carotenoids, flavonoids, lipids and waxes, polyphenols, proteins, steroids, tannins and triterpenes.	[1,73]
Clerodendron inerm	Antiviral	-	Carboxylic acids, diterpenes, flavonoids, hydrocarbons, iridoid bigylcoside, neolignans, phenols, protein, steroids, triglycerols and triterpenes.	[1]
Diospyros cordifolia	Antifungal	-	Alkaloids, flavonoids, naphthoquinones, saponins and tannins.	[1]
Dolichandrone spathaceae	Antibacterial Anti fungal	-	Napthoquinones , triterpene and saponin.	[29,28]
Excoecaria agallocha	Antiviral, Antibacterial Antifungal	**Fungus** (*Phomopsis* sp) and **endophytic bacteria**	Alkaloids, carotenoids, chalcones, cyclitol, diterpenes, excoecaria toxins, fluratoxin, glycerides of fatty acids, lipids and waxes, phorbol esters, polyphenols, polysaccharides, proteins, saponins, steroids, sugars, tannins, triterpenes, phomopsin A , B, C and , cytosporon B and C.	[58,39,33]

Fagara zanthoxyloides	Antibacterial	-	Alkaloids, phenols and tannins.	[1, 67]
Heritiera littoralis and *H.fomes*	Antifungal Antibacterial	**Endophytic fungi**	Alkaloids, aminoacida, carbohydrates, carotenoids, tannins, fatty acids; flavonoids, lipids and waxes; polyphenols, polysaccharides, proteins, saponins, sesquiterpenes, aliphatic carboxylic acids, sugars.	[27,63]
Kandelia candel	Antibacterial	**Endophytic fungi** and **bacterium** (*Streptomyces* sp).	Sesquiterpenes, kandenols alkaloids, benzoquinones, carbohydrates, carotenoids, flavonoids, inorganic salts, polyphenols, proteins, tannins, saponins, short chain aliphatic carboxylic acids and sugars.	[1,63,68]
Lumnitzera racemosa	Antiviral	**Endophtic fungi**	Cyclitols, sugars and tannins.	[1,69]
Melaleuca leucadendron	Antifungal Antiviral	**Endophytic fungi** and **bacterium** (*Streptomyces* sp).	Tannins, mono- di- and triterpenes, sesquiterpenes, polyphenols, proteins, stilbenes and stilbene glycosides.	[1,70,71]
Pongamia pinnata	Antibacterial Antiviral Antifungal	**Endophytic Acsomycetes**	Amino acids, chalcones and chromones, fatty acids; flavones and flavone glycosides, indole-3-acetic acid, lipids, monoglycerides, phenyl propanoids, proteins, sugars and tannins,	[1]
Rhizophora apiculata	Antiviral, Antifungal	**Endophytic fungi**	Aliphatic alcohols aldehydes, and carboxylic acids, carotenoids, condensed and hydrolysable tannins, benzoquinones, lipids, n-alkanes, minerals, phenolic compounds, polysaccharides, steroids and triterpenes.	[72,58,73]
Rhizophora mucronata	Antiviral, antibacterial	**Fungus** *Hypocrea lixii*	Alkaloids, anthocyanidins, carbohydrates, carotenoids, tannins,gibberellins, flavonoids,inositols, lipids, polysaccharides, polyphenols,procyanidins, proteins, saponins,steroid and triterpenes.	[1,9]
Salicornia brachiata	Antiviral Antibacterial	**Endophytic *Actinomycetes***	Alkaloids, flavonoids, tannin, polyphenolics and oil.	[74,75,1,47]
Sesuvium portulacastrum	Antibacterial Antifungal	**Endophytic bacteria**	Fatty acid methyl esters.	[76,33]
Suaeda maritima	Antibacterial	**Endophytic bacteria**	Proteins, Tannins, alkaloids carbohydrates and flavonoids.	[77,33]
Sonneratia caseolaris	Antibacterial Antifungal	**Fungus** *Bionectria ochroleuca*	Peptide pullularins A,C,E and F and verticilli D,flavonoids, triterpenoids, cardiac glycosides and alkaloids.	[37,78]
Sonneratia alba	Antibacterial	**Fungus** *Alternaria* sp	Alternarian acid, altenusin, altenuene , 4'-epialtenuene ,alternarienonic acid , alternariol and altertoxin.	[79]
Thespesia populnea	Antibacterial	**Endophytic fungi**	Amino acids, carbohydrates, glycerides and glycosides, gossypol, fatty acids, mansonones, phenolic sesquiterpenes, phytolectins, organic acids, triterpenes, quinones and sterols.	[1,80]
Xylocarpus granatum	Antibacterial Antifungal	**Endophytic fungi**	Protoxylogranatin B**,** alkaloids, amino acids, carbohydrates, carotenoids, fatty acids, flavonoids, hydrocarbons; limonoids, organic acids; polyphenols, proteins, tannins, triterpenes, saponins, steroids and sugars.	[1,81,22]

5. Conclusion

Mangrove plants thrive under extreme environment which lead to the development of special metabolic pathways to produce unique chemicals that enable them to tolerate such stressful environmental conditions. Some of these chemicals are confirmed to be of great potential as a source of novel agents for various pharmaceutical and other industerial applications.

Several reports have clearly indicated the isolation of effective antimicrobial agents from some of the mangrove and mangrove associated plants. These discoveries highlight the importance of mangrove as a valuable source of natural chemical agents with interesting pharmacological properties that require more efforts to discover them and to validate their efficiency.

Endophytes are microorganisms that live in the intercellular spaces of plant tissue with no apparent damage to their host. Endophytes represent a huge diversity of microbial adaptations that have developed in special sequestered environment. A number of endophytic –derived bioactive agents have been isolated and characterized. A great number of these isolates were shown to be antimicrobials.

Bacteriocins are specific and highly potent proteins with antimicrobial properties that have gained more attention recently as new molecules with interesting pharmacological properties. Great efforts have been made in recent years to unravel the production of bacteriocins- like inhibitory substances from different bacterial groups including bacterial endophytes. Research in this field has been fuelled by massive genome sequencing and the development in the related field of molecular biology in general which allow the detection of new bacteriocins and to evaluate the distribution of key enzymes involved in bacteriocin synthesis. This may lead to a better understanding of the significance of bacterial antagonism mediated by antimicrobial peptides in nature.

More new natural products of varied chemical structures are continually being reported from endophytic microorganisms. Endophytes therefore, are viewed as an outstanding source of bioactive natural products with interesting bioprospecting potentiality that need to be fully discovered.

Our research group in the Institute of Marine Biotechnology (IMB), University Malaysia Terengganu, are currently focusing (project in progress) on isolation and identification of bacteriocin like inhibitory substances from bacterial endophytes isolated from some Malaysian mangrove plants.

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