Journal of Tropical Biodiversity and Biotechnology
Volume 07, Issue 02 (2022): jtbb69913
DOI: 10.22146/jtbb.69913

Review Article

Pharmacological Maneuver of Mangrove Endophytic Fungi in the South China Sea – A review

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Keywords:
biological activities
mangrove endophytic fungi
metabolites
South China sea
Submitted:
22 October 2021
Accepted:
27 January 2022
Published:
23 May 2022
Editor:
Miftahul Ilmi

ABSTRACT
Conventional products have a role in addressing the thriving universal demands for biologically active substances. Since the South China Sea is a prodigious province of geostrategic and mercantile importance, it meets the basic needs of people who dwell there. The South China Sea is dominant in mangrove biodiversity which, represents 11.4% of the world's 15.5 million hectares of mangrove forest. Mangroves are harbored by multifaceted fungal communities that represent the second colossal ecological breed of marine fungi. The symbiotic association between the plants and fungi stimulates the bioactive components such as alkaloid, depsipeptides, cyclic peptides, quinone, terpenes, lactones, terpenoid, flavonoid, phenolic acid, steroids. These components have multifaceted pharmacological activities likely, anti-inflammatory, antidiabetic, anticancer, antioxidant, and antimicrobial. This review article attempts to present a piece of insightful information currently being explored on the biologically active components generated by mangrove endophytic fungi of the South China Sea.

INTRODUCTION
People experience multifaceted maladies that devastate their health. Several synthetic and natural therapy are available to curb and treat these diseases. Utmost people globally entrusted natural medicine than synthetic due to its minimal side effects and cost-effectiveness. Hitherto, plants and microbes are appraised to be a root source of natural medicine. Ethnopharmacological proficiency provides the unrivaled groundwork for the future endeavor of medicinal expedients in traditionally used plants. With the aid of advanced technologies, researchers can identify, isolate and extract an enormous number of new components from natural resources. From 1981 to date, merely 50% of anti-microbial drugs are in the practice of the pharmacy market. Roughly 75% of it is from natural or derivates of natural products (Salini 2015). However, increased demand for commercially successful natural products causes an overwhelm of plant material to produce an adequate quantity of drugs, which has engendered threat concerns like species extinction, biodiversity loss, and environmental depletion. These jeopardized situations kindle the researcher to scrutinize and isolate Taxol (cancer drug) producing endo-

phytic fungi *Taxomyces andreanae* which gave an alternative route to acquire an inexpensive and readily affordable product *via* fermentation of microorganisms (Bibi et al. 2020). Based on the existing literature survey signify that plant endophytes can inherit the secondary metabolites of the host. Enormous metabolites extracted from the endophytic fungi of mangrove species emerged mainly from the South China Sea (SCS). These components show various remarkable biological activities, namely anticancer, antimicrobial, anti -inflammatory, antidiabetic, and antioxidant, which have biotechnology exploitation in the field of pharmacy. In this survey article, we endeavor to explore the insightful benefits of the biologically active components generated by mangrove endophytic fungi of the SCS.

MANGROVES - SCS REGION

The SCS is one of the vast marginal seas of the Western Pacific Ocean, bordering a region of approximately 3,500,000 km² (1,400,000 sq mi) (Anon 2008). It is a province of prodigious mercantile and geostrategic that meets the basic need of two hundred and seventy million people dwelling on the border nations of SCS. Mangroves, seagrass meadows, and coral reefs are the most dominant coastal ecosystems of the SCS. South China Sea is considered one of two global hotspots of mangrove biodiversity. The total area of mangrove species on the SCS coast of all countries (Brunei, Cambodia, China, Indonesia, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam) are consolidated as 1.77 million hectares, representing 11.4% of the world's mangrove forest (FAO 2007; Vo et al. 2013). Mangrove, known as halophytes, grows in the coastal saline or brackish waters in rocky or muddy soils. The presence of pneumatophores (*Bruguiera gymnorhiza* (L.) Lam.) and rhizophores system (*Rhizophora mucronata* Lam.), provides structural support for the plants to adapt to the harsh coastal condition (Tomlinson 1994). Mangrove produces outstanding natural resources on their own due to the inhabitants of the transition zone between land and sea.

Mangrove forests are rich in different types of flora and fauna. The prime genera are *Lumnitzera* and *Laguncularia* (Combretaceae), *Nypa* (Palmae), *Avicennia* (Avicenniaceae), *Kandelia* and *Rhizophora* (Rhizophoraceae), and *Sonneratia, Bruguiera, Ceriops* (Sonneratiaceae) (Tomlinson 1994). Due to frequent flooding of the tidal wave, mangrove resilience with environmental cues and also loaded with the surplus of nutrients to serve a myriad of heterogenetic habitats including microorganisms such as epiphytes and endophytes (Sridhar 2019; Thatoi et al. 2020). Until now, plant species of mangrove have greatly been conventionally used for therapeutical purposes as a treatment against a broad range of ailments namely snake bites, hypertension, toothache, oral infection, diabetes, hematuria, hepatitis, diarrhea, constipation, fever, dysentery, rheumatism, dyspepsia, among others. Carotenoids, catechins, procyanidins, gibberellins, gallic acid, isorhamnetin, isocoumarin, among others, are the several phytoconstituents segregated from mangrove plants that were explored for diverse biological activities (Salini 2015).

MANGROVE ENDOPHYTIC FUNGI

The microscopic community of microorganism is hidden and reside within the plant known as endophytes. Endophytes (actinomycetes, bacteria, fungi) spend their life cycle entirely or partially in the tissues of the plants that cause no menace to the plant. Plants harbor a varied cluster of endophytes ubiquitously distributed in roughly 300,000 plant species (Sridhar 2019). The endophyte symbiotically associated with the plants are knowns as symbionts. Moreover, the endophytic colonies are beneficial to our surroundings. For instance, endophytes aid the plants to flourish by generating growth hormones, nutrient cycling, biodegrading. It also takes part in phytoremediation that reduces detritus load in our landscape (Das et al. 2018).

Mangroves are harbored by versatile fungal communities, which account for the second colossal ecological breed of marine fungi. Mangrove endophytic fungi are robustly resistant to oceanic environments, temperature for example, *Alternaria*, *Aspergillus*, *Cladosporium, Clolletotrichum*, *Fusarium, Paecilamyces, Penicillium*, *Pestalotiopsis*, *Phomopsis*, *Phyllosticta*, and *Trichoderma* (Bibi et al. 2020). Repeated flooding and drastic climatic fluctuation make the mangrove plant resilient both physiologically and morphologically. This acclimatization engenders the plant to generate a broad spectrum of biologically active secondary metabolites. Endophytes were grown in such an ecosystem with a unique nature that produces remarkable secondary metabolites such as flavonoids, quinones, alkaloids, terpenoids, tetralones, benzopyranones, xanthones among others. The plant-endophyte association generates bioactive components with promising pharmacological effects such as antioxidant, anticancer, and antimicrobial properties (Das et al. 2018).

BIOACTIVE METABOLITES OF MANGROVE ENDOPHYTES

Unrivaled research of plants and microbes generates a trove of novel natural products that act as happening and growing demand to curb diverse aliments. Multifarious biologically active metabolites have been extracted and identified from fungi habitats around countries bordering the South China Sea. Thatoi et al. (2020) stated that enzymes extracted from the mangrove endophytes have an ecological role in the decomposition and a bioactive role towards the medical environment. Secondary metabolites obtained from these endophytes have an efficient role in mitigating various ailments which have bioactive potential in both the medical and pharmaceutical fields. Camptothecin, Irinotecan, Podophyllotoxin, Taxol, Vinblastine, Vincristine are the commercially available metabolites among them (Bibi et al. 2020).

With the evolution of the latest modern technologies, such as chromatographic and spectroscopic techniques, CD spectra analysis, in-vitro bioassay methods, and nuclear magnetic resonance (NMR), researchers can skillfully perform mangrove fungal isolation, cultivation, and extraction of captivating beneficial bioactive metabolites (Perera et al. 2019). Endophytes produce versatile secondary metabolites such as isocoumarins, xanthones, lactones, and ergosterl with antimicrobial properties that preclude the plants

from pathogens (Sridhar 2019). Several comprehensive types of research have been carried out in the last decades, related to the characterization and isolation of metabolites from the mangrove endophytic fungi. Liu et al. (2016) recognized polyketides from *Penicillium* sp. ZJ-SY2 endophytic fungus of mangrove which shows an immunosuppressive activity. Li et al. (2019) extracted polyketide alkaloid derivatives namely phomopsols A and B from the *Phomopsis* sp. xy21 endophytic fungus of mangrove. Liu et al. (2018) obtained polyketide (1) from the endophyte A*scomycota* sp. SK2YWS-L conducts an anti-inflammatory activity. One new natural amide alkaloid and two new benzophenones are identified by Zheng et al. (2019) from *Penicillium citrinum* mangrove fungus that has an antibacterial property against *Staphylococcus aureus* and shows strong cytotoxic action against A549 human cell lines. Chen et al. (2019) obtained ascomylactams A-C metabolites from the endophyte *Didymella* sp. CYSK-4 of mangrove that performs average cytotoxicity towards HCT116, MDA-MB-435, PC-3, NCI-H460, MDA-MB-231, and SNB19. From these discussions, we can drive that those endophytic fungi extracted from the mangrove species are the prime origin of bioactive metabolites and requires further studies for other feasibilities.

BIOLOGICAL ACTIVITIES OF MANGROVE ENDOPHYTES

An endophytes-plants symbiotic relationship activates the inheriting properties of the bioactive compounds of the host. They are the warehouse of novel bioactive secondary metabolites that possess various biological applications in the pharmaceutical field, likely anticancer, anti-inflammatory antidiabetic, and antioxidant. Table 1 represent the metabolites generated from the mangrove endophytic fungi of the SCS and their bioactive significance. Figure 1 depict the pharmacological benefits of secondary metabolites of mangrove endophytes.

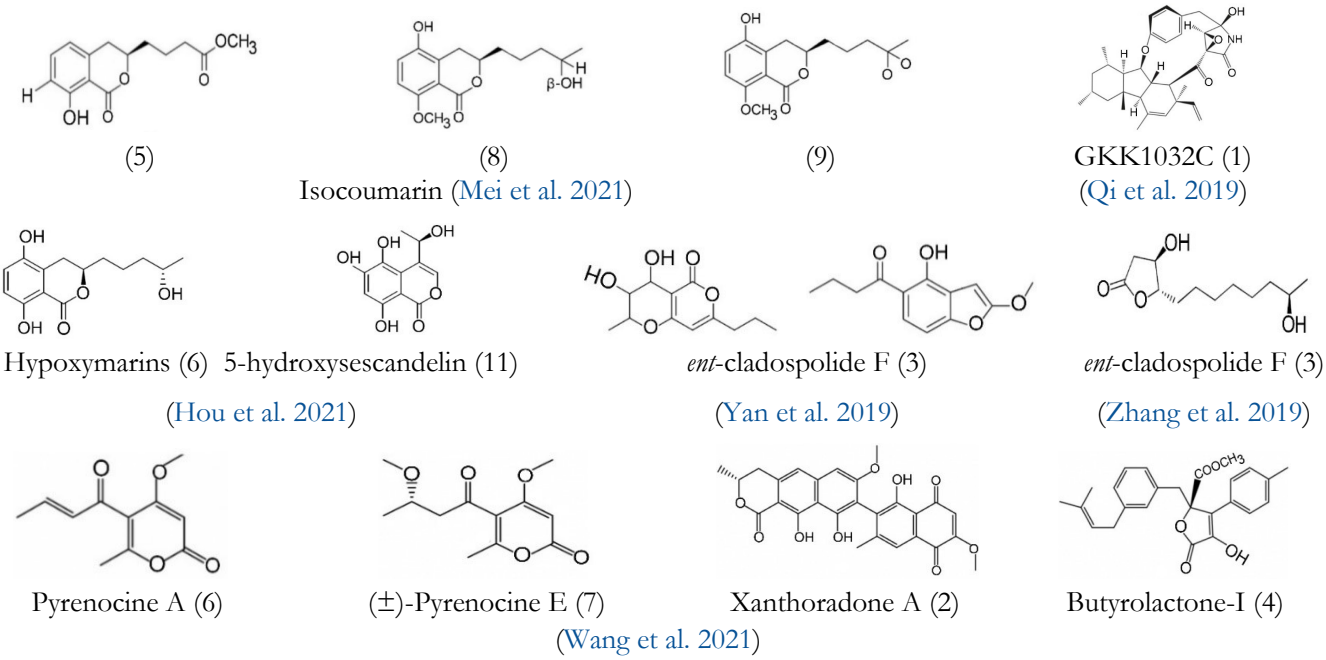

Figure 1. Bioactive metabolites isolated from mangrove endophytic fungi.

Table 1. Bioactive metabolites and their pharmacological applications omangrove endophytic fungi.

Endophytic fungi	Mangrove plant	Bioactive metabolites and Activities	References
		Cytotoxic effects	
Aspergillus sp. HN15-5D	*Acanthus ilicifolius*	Aspergisocoumrins A (1) (IC_{50} = 5.08 ± 0.88 μM) and aspergisocoumrins B (2) (IC_{50} = 4.98 ± 0.74 μM) showed cytotoxicity in oppose to cancer cell line of MDA-MB-435.	Wu et al. 2019
Aspergillus sydowii #2B	*Aricennia marina*	Butyrolactone I (4) (IC_{50} = 1.92 ± 0.82 μM), pyrenocine S (5) (IC_{50} = 20.06 ± 2.01 μM), pyrenocine A (6) (IC_{50} = 7.92 ± 0.86 μM) and pyrenocine E (7) (IC_{50} = 10.13 ± 0.88 μM), (þ)-3,30 ,7,70 ,8,80 -hexahydroxy-5,50 -dimethyl-bianthra-quinone (3) (IC_{50} = 33.36 ± 1.42 μM), xanthoradone A (2) (IC_{50} = 4.19 ± 1.02 μM), showed potent cytotoxicity's towards prostate cancer VCaP cell line.	Wang et al. 2021
Penicillium citrinum HL-5126	*Bruguiera sexangula* var. *rhynchopetala*	Penibenzophenones B (2) (IC_{50} = 15.7 μg/mL) has cytotoxicity that resists human cell line A549.	Zheng et al. 2019
Penicillium sp. J-54	*Ceriops tagal*	Penicieudesmol B (2) (IC_{50} = 90.1 μM) exhibits minimal cytotoxicity inhibition of the human K-562 cell line.	Qiu et al. 2018
Cladosporium sp. HNWSW-1	*Ceriops tagal*	Cladosporitins B (2) exhibit cytotoxicity resist towards cell lines BEL-7042 (IC_{50} = 29.4 ± 0.35 μM), K562 (IC_{50} = 25.6 ± 0.47 μM) and SGC-7901 (IC_{50} = 41.7 ± 0.71 μM), whereas talaroconvolutin A (4) against cancer cell lines Hela (IC_{50} = 14.9 ± 0.21 μM) and BEL-7042 (IC_{50} = 26.7 ± 1.1 μM).	Wang et al. 2018
Cytospora sp.	*Ceriops tagal*	Integracin A (4) (IC_{50} = 5.98 ± 0.12 μM) and Integracin B (5) (IC_{50} = 9.97 ± 0.06 μM) has a cytotoxicity effect that opposes HepG2 cancer cell line.	Wei et al. 2020
Trichoderma sp. 307	*Clerodendrum inerme*	Botryorhodine H (1) has a potent cytotoxic that oppose cell lines of rat pituitary adenoma GH3 (IC_{50} = 3.64 μM) and rat prolactinoma MMQ (IC_{50} = 3.09 μM).	Zhang et al. 2018
Cladosporium sp. OUCMDZ-302	*Excoecaria agallocha*	New polyketide compound (6) (IC_{50} = 10.0 μM) has cytotoxicity that hinders the H1975 cell line.	Wang et al. 2018
Didymella sp. CYSK-4	*Pluchea indica*	Ascomylactams A (1) and C (3) have average cytotoxicity towards the human cancer cell lines such as HCT116, MDA-MB-435, PC-3, MDA-MB-231, SNB19, and NCI-H460 (IC_{50} range from 4.2–7.8 μM).	Chen et al. 2019
Aspergillus fumigatus HQD24	*Rhizophora mucronata*	1,11-dideacetyl-pyripyropene A (2) cytotoxic activities.	Zou et al. 2021
Phoma sp. SYSU-SK-7	*Kandelia candel*	Colletotric B (2) and analog (1) (IC_{50} values range between 16.82 - 37.73 μM) also showed cytotoxicity against human cancer cell lines A549 and MAD -MB -435.	Chen et al. 2019
Streptomyces sp.	Rhizosphere of *Kandelia candel* and *Excoecaria agallocha*	Non-ribosomal peptide synthetase, type-I polyketide synthase, and type-II polyketide synthase are the enzymes that show cytotoxic activities against CNE-2 and Hela.	Gong et al. 2018
Pseudopithomyces sp. 1512101	*Sonneratia caseolaris*	Phospholipase A_2 (PLA_2) Anti-cancer activity against A549, SH-SY5Y, and HeLa cells.	Wei et al. 2021
		Antimicrobial effects	
Phomopsis sp. HNY29-2B.	*Acanthus ilicifolius*	α-pyrone derivative, compounds (2) (MIC = 25 μM) and (3) (MIC = 50μM) reveal the least antibacterial activities against *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and *Bacillus subtilis*.	Cai et al. 2017

Table 1. Contd.

Talaromyces stipitatus SK-4	*Acanthus ilicifolius*	Talaromyones B (2) (MIC = 12.5 µg/mL) shows a potent antibacterial activity against *Bacillus subtilis*.	Cai et al. 2017
Epicoccum nigrum SCNU-F0002	*Acanthus ilicifolius* L	New polyketides compounds (6 and 7) showed antibacterial effects against *Bacillus subtilis* (ATCC 6538), *Escherichia coli* (ATCC 8739), and *Staphylococcus aureus* (ATCC 6538), with MIC ranging between 25–50 µg/mL.	Yan et al. 2019
Phomopsis longicolla HL-2232	*Brguiera sexangula* var. *rhynchopetala*	New biphenyl derivative 5,5'-dimethoxybiphenyl-2,2'-diol (1) show a moderate inhibition on *Vibrio parahaemolyticus* (MIC = 10 µg/mL), altersolanol B (4) antibacterial activities against *Vibrio parahaemolyticus* (MIC = 2.5 µg/mL) and *Vibrio anguillarum* (MIC = 5 µg/mL).	Li et al. 2017
Daldinia eschscholtzii HJ001	*Brguiera sexangula* var. *rhynchopetala*	New cytochalasin (1) (MIC = 50 µg/mL) as [11] cytochalasa-5(6),13-diene-1,21-dione-7,18-dihydroxy-16,18-dimethyl10-phenyl-(7S*,13E,16S*,18R*) shows least antibacterial towards *Vibrio alginolyticus, Vibrio parahaemolyticus, Bacillus cereus Staphylococcus aureus,* and *Escherichia coli.*	Yang et al. 2018
Ascomycota sp. CYSK-4	*Pluchea indica*	Dichlorodiaportintone (1), desmethyldichlorodiaportin (5), and dichlorodiaportin (6) (MIC ranging between 25- 50 µg/mL) show an antibacterial property against *Klebsiella pneumoniae, Staphylococcus aureus, Bacillus subtili, Acinetobacter calcoaceticus, and Escherichia coli.*	Chen et al. 2018
Cladosporium cladosporioides MA-299	*Bruguiera gymnorrhiza*	Polyketides *ent*-cladospolide F (3) (MIC = 8.0 µg/mL) exhibit average inhibitory against human pathogenic bacteria *Staphylococcus aureus,* cladospolide G (4) (MIC = 1.0 µg/mL) strong inhibitory against plant pathogen *Fusarium oxysporum and Glomerella cingulat.* Compounds (7) - exhibited antimicrobial activity against plant pathogen *Glomerella cingulat* (MIC = 4.0 µg/mL) and aquatic bacterium *Edwardsiellaictarda* (MIC = 1.0 µg/mL).	Zhang et al. 2019
Penicillium citrinum HL-5126	*Bruguiera sexangula* var. *rhynchopetala*	Penibenzophenones A (1) (MIC = 20 µg/mL) - antibacterial against *Staphylococcus aureus.*	Zheng et al. 2019
Cladosporium sp. JJM22	*Ceriops tagal*	(3S)-3,8-dihydroxy-6,7-dimethyl-αtetralone (3) (MIC = 20 µM) - reveal a wide range of antibacterial against *Vibrio parahemolyticus, Escherichia coli, Staphylococcus aureus, Bacillus cereus,* and *Vibrio alginolyticu.*	Wu et al. 2019
Cladosporium sp. JS1-2	*Ceriops tagal*	Pentenoic acid derivative compounds (1) (MIC = 25.0 µg/ml), (2) (MIC = 12.5 µg/ml), (4) (MIC = 6.25 µg/ml), (6) (MIC = 1.25 µg/ml) and (7) (MIC = 6.25 µg/ml) showed average antibacterial activity oppose to *Staphylococcus aureus.*	Bai et al. 2019
Cytospora sp.	*Ceriops tagal*	Cytospomarin (2) (MIC = 0.35 µM) feeble inhibition of *Escherichia coli* (GIM1.201).	Wei et al. 2020
Penicillium commune QQF-3	*Kandelia candel*	Peniisocoumarins G (7) (IC_{50} = 20.7 µM) Mycobacterium tuberculosis protein tyrosine phosphatase B (MptpB).	Cai et al. 2018
Aspergillus sp. ZJ-68	*Kandelia candel*	Asperophiobolins H (8) (IC_{50} = 19 µM) was found to have significant inhibition of Mycobacterium tuberculosis protein tyrosine phosphatase B (MptpB).	Cai et al. 2019
Aspergillus sp. 085242	Mangrove plant	Racemate (3) showed antibacterial activity against *Salmonella.*	Guo et al. 2020

Table 1. Contd.

Aspergillus sp. xy02	*Xylocarpus moluccensis*	(7S,10S)-7,10-epoxysydonic acid (2), (7R,11S)-7,12-epoxysydonic acid (3), 7-deoxy-7,14-didehydro-12-hydroxysydonic acid (5), (E)-7-deoxy-7,8-didehydro-12-hydroxysydonic acid (7), and analogues (9-12) with IC_{50} range between 31.5 - 41.9 µM that exhibit medium resist action towards *Staphylococcus aureus* ATCC 25923.	Wang et al. 2018
Talaromyces sp. HZ-YX1	*Kandelia obovata*	Talaramide A (1) (IC_{50} = 55 µM) - showed active inhibitory of mycobacterial PknG.	Chen et al. 2017
Aspergillus sp. ZJ-68	*Kandelia candel*	2-(hydroxymethyl)-3-propylphenol (8) and brassicadiol (11) indicate an opposing activity to strains *Escherichia coli, Bacillus subtilis* and *Staphylococcus aureus*, with MIC values ranging between (4.15 - 12.5 µg/mL).	Cai et al. 2019
Pestalotiopsis sp. HHL101	*Rhizophora stylosa*	Pestalotiopisorin B (1) exhibit average antibacterial inhibition of *Escherichia coli* (MIC =12.5 µg/ml) and *Pseudomonas aeruginosa* (MIC =50 µg/ml).	Xu et al. 2020
Streptomyces sp.	Rhizosphere of *Kandelia candel* and *Excoecaria agallocha*	Nonribosomal peptide synthetase, type-I polyketide synthase, and type-II polyketide synthase reveal antibacterial against *Bacillus cereus* ATCC 14579 and *Escherichia coli* ATCC 13706, *Staphylococcus aureus* SA115 and *Enterococcus faecium* EF009	Gong et al. 2018
Leptosphaerulina sp. SKS032	*Acanthus ilicifolius*	Leptospyranonaphthazarin A (1) (MIC = 25.0 µg/mL) and leptosnaphthoic acid A (2) (MIC = 50.0 µg/mL) and compound (6) (MIC = 50.0 µg/mL), exhibit minimal antibacterial activities resist to *Staphylococcus aureus*.	Cui et al. 2017
Phoma sp. SYSU-SK-7.	*Kandelia candel*	Colletotric B (2) and analog compounds (1) (MIC range between 1.67–6.28 µg/ml) have an efficient antimicrobial inhibition of MRSA, *C. albicans* and *P. aeruginosa*.	Chen et al. 2019
Penicillium sp. CPCC 400817	*Ceriops tagal*	GKK1032C (1) (MIC = 1.6 µg/ml), manifest strong antibacterial activity against MRSA.	Qi et al. 2019
Cladosporium sp. JJM22	*Ceriops tagal*	(3S)-3,8-dihydroxy-6,7-dimethyl-αtetralone (3) (MIC = 20 µM) - indicate wide range of antibacterial action against MRSA.	Wu et al. 2019
		Anti-diabetic effects	
Talaromyces stipitatus SK-4	*Acanthus ilicifolius*	Talaromyones B (2), purpactin A (4), and tenellic acids A (5) have an inhibition action towards α-glucosidase enzyme activity IC_{50} range between 48.4 - 99.8 µM	Cai et al. 2017
Penicillium commune QQF-3	*Kandelia candel*	Peniisocoumarins C (3), G (7), I (9), and J (11) reveal average α-glucosidase inhibition with IC_{50} range between 38.1 - 78.1 µM.	Cai et al. 2018
Lasiodiplodia theobromae ZJ-HQ1	*Acanthus ilicifolius*	Lasiodiplactone A (1) **(**IC_{50} = 29.4 µM**)** shows a potent α-glucosidase enzyme inhibition.	Chen et al. 2017
Hypoxylon sp. Hsl2-6	*Bruguiera gymnorrhiza*	Diterpenoids and isocoumarin derivatives hypoxyterpoids (1) (IC_{50} = 741.5 ± 2.83 µM) manifest a moderate α-glucosidase inhibitory activity.	Hou et al. 2021
Mycosphaerella sp. SYSU-DZG01	*Bruguiera gymnorrhiza*	Asperchalasine I (1) (IC_{50} = 17.1 µM), epicoccolide B (8**)** **(**IC_{50} = 26.7 µM**)** and asperchalasine A (9) (IC_{50} = 15.7 µM) indicate potent α-glucosidase enzyme inhibition.	Qiu et al. 2019
Trichoderma sp. 307	*Clerodendrum inerme*	Botryorhodines H (1), C (2), and D (3) (IC_{50} range between 8.1 - 11.2 µM) reveal α-glucosidase enzyme inhibition.	Zhang et al. 2018
Cladosporium sp. JJM22	*Ceriops tagal*	Cyclohexene derivatives cladoscyclitols B (2) (IC_{50} = 2.95 µM) and 4- *O* -α-D-ribofuranose-2-pentyl-3-phemethylol (5) (IC_{50} = 2.05 µM) signify α-glucosidase enzyme inhibition.	Zhang et al. 2021

Table 1. Contd.

Penicillium sp. YYSJ-3	*Heritiera littoralis*	Isocoumarin derivatives compounds (3) (IC_{50} = 100.6 µmol/L), (6) (IC_{50} = 133.4 µmol/L) and (7) (IC_{50} =130.9 µmol/L) indicate promising inhibitory activity against α-glucosidase.	Qiu et al. 2020
Aspergillus sp. 085242	Mangrove plant	Asperisocoumarin G (1) **(**IC_{50} = 392.4 µmol/L**)** and pergillin (4) (IC_{50} = 428.1 µmol/L**)** have a medium *a*-glucosidase enzyme inhibitory action.	Guo et al. 2020
Aspergillus flavus QQSG -3	*Kandelia obobata*	Compounds (3, 5, 10, and 11) (IC_{50} values range between 1.5 - 4.5 µM) are phenolic bisabolane sesquiterpenoid possess strong α-glucosidase inhibitory effects.	Wu et al. 2018
Aspergillus sp. ZJ-68	*Kandelia candel*	Phenylpropanoid derivatives compound (6) (IC_{50} = 12.4 µM) reveal potent inhibitory activity against α -glucosidase.	Cai et al. 2019
Talaromyces sp. CY-3	Semi-mangrove *Hibiscus tiliaceus*	Sambutoxin derivatives sambutoxin A (1), sambutoxin B (2), sambutoxin C (3), ilicicolin H (4), deoxyleporin B (5) with IC_{50} =12.6 ± 0.9 - 57.3 ± 1.3 µM possess an α-glucosidase inhibitory action.	Yang et al. 2021
Cladosporium sp. HNWSW-1	*Ceriops tagal*	Talaroconvolutin A (4) (IC_{50} = 78.2 ± 2.1 µM) and anthraquinone (5) (IC_{50} = 49.3 ± 10.6 µM) have an enzyme inhibitory action towards α-glycosidase.	Wang et al. 2018
Penicillium sp. MGP11	*Xylocarpus granatum*	New isocoumarins namely penicimarin I (5) (IC_{50} = 776.5 µM), penicimarin G (8) (IC_{50} = 683.7 µM) and penicimarin H (9) (IC_{50} = 868.7 µM) reveal an α -glucosidase enzyme inhibition.	Mei et al. 2021
Phoma sp. SYSU-SK-7	*Kandelia candel*	Phomosterols A (1) (IC_{50} = 51.2 µM), B (2) (IC_{50} = 46.8 µM) own a potent *a*-glucosidase enzyme inhibition.	Chen et al. 2020
Phoma sp. SYSU-SK-7	*Kandelia candel*	Colletotric B (2), colletotric C (4), 3 -hydroxy5 -methoxy-2,4,6 -trimethylbenzoic acid (3), and analog (1 and 5) (IC_{50} values range between 36.2–90.6 µM) signify α-glucosidase enzyme inhibition.	Chen et al. 2019
		Anti-inflammatory effects	
Aspergillus sp. GXNU-MA1	*Acanthus ilicifolius*	New sesquiterpene, gxsespene A (1), and compounds (2-5) **(**IC_{50} range between 16.15 - 27.08 µM) possess an anti-inflammatory property by preventing NO secretion in LPS triggered RAW264.7 cells.	Zhou et al. 2020
Aspergillus sp. GXNU-A9	*Acanthus ilicifolius*	Guanxidone A (1) (IC_{50} value of 8.22 µM) owns an anti-inflammatory property by reducing the NO generation in LPS influenced RAW 264.7 macrophage.	Hao et al. 2020
Aspergillus sydowii #2B	*Aricennia marina*	Compounds 2-(12S-hydroxypropyl)-3-hydroxymethyl-6-hydroxy-7-methoxychromone (1) (IC_{50} = 40.15 µM, (þ)-3,30 ,7,70 ,8,80 -hexahydroxy-5,50 -dimethyl-bianthra-quinone (3) (IC_{50} = 28.69 µM), pyrenocine A (6) (IC_{50} = 25.25 µM), and pyrenocine E (7) (IC_{50} = 43.08 µM) signify minimal inhibitory effects on NO secretion in LPS influenced RAW 246.7 cells.	Wang et al. 2021
Aspergillus sp. ZJ-68	*Kandelia candel*	Asperophiobolins H (8) I (9) J (10) and analogs (14–17) (IC50 range between 9.6 - 25 µM) has an opposing action of NO generation in LPS triggered RAW 264.7 macrophage cells.	Cai et al. 2019
Ascomycota sp. SK2YWS-L	*Kandelia candel*	Ascomindone D [(+)-1 (IC_{50} = 17 µM) and (-)-1 (IC_{50} = 17.1 µM) reveals a significant anti-inflammatory by hindering against the NO oozing in LPS promoted RAW 246.7 mouse.	Liu et al. 2018

Table 1. Contd.

Phomopsis sp. SYSU-QYP-23	*Kandelia candel*	Compounds (3–9) namely, farinomalein H (3) indole alkaloid phomoamide (8), and analog compounds (4-7) and (9) (IC_{50} values ranging between 4.5 - 25 µM) of five new maleimide derivatives reveal inhibitory action against NO generation in LPS stimulated RAW 264.7 cells.	Chen et al. 2020
Phomopsis sp. SYSU-QYP-23	*Kandelia candel*	Eight new sesquiterpene derivatives compounds (1 –7) (IC_{50} values ranging between 8.6 to 14.5 µM) potent resistance to NO discharge in LPS influenced RAW 264.7 cells.	Chen et al. 2021
Talaromyces amestolkiae YX1	*Kandelia obovata*	Amestolkolide (B) (IC_{50} = 1.6 ± 0.1 µM) exhibits sturdy anti-inflammatory activity by inhibiting NO production in LPS triggered in RAW264.7 cells.	Chen et al. 2018
Diaporthe sp. QYM12	*Kandelia candel*	Diaporpenoids A (1) (IC_{50} = 21.5 µM) and diaporpyrones A (4) (IC_{50} = 12.5 µM) showed effective anti-inflammatory activities by resisting the generation of NO in LPS- triggered RAW264.7 cells.	Chen et al. 2021
Penicillium citrinum QJF-22	*Kandelia candel*	Benzopyran derivatives 3R,4S)-3,4,8-Trihydroxy-3,4-dihydronaphthalen-1(2H)-one (IC_{50} = 44.7 µM) signify feeble resistance effects on LPS-induced NO production in RAW264.7 cells.	Yang et al. 2020
Ascomycota sp. CYSK-4	*Pluchea indica*	Desmethyldichlorodiaportintone *(2) (*IC_{50} = 15.8 µM*)* indicattes effective inhibiting of the generation of NO in LPS stimulated RAW 264.7 cells.	Chen et al. 2018
Phomopsis sp. 33#	*Rhizophora stylosa*	Chromenopyridines derivatives (3) *(*IC_{50} = 49.0 µM*)* and (4) *(*IC_{50} = 51.0 µM*)* showed average inhibition of nitric oxide generation in LPS induced RAW 264.7 cells.	Chen et al. 2018
Aspergillus fumigatus HQD24	*Rhizophora mucronata*	1,11-dideacetyl-pyripyropene A (2) immunosuppressive activity.	Zou et al. 2021
Phomopsis sp. xy21	*Xylocarpus granatum*	Phomopsol A (1) and polyketide-derived (3) neuroprotective effects.	Li et al. 2019
Phoma sp. SYSU-SK-7	*Kandelia candel*	Phomosterols A (1) (IC_{50} = 13.5 µM), B (2) (IC_{50} = 25.0 µM) and neocyclocitrinol B (5) (IC_{50} = 12.5 µM) hinder NO production in LPS triggered RAW 264.7 cells.	Chen et al. 2020
		Anti-oxidant effects	
Epicoccum nigrum SCNU-F0002	*Acanthus ilicifolius* L	Compounds (10) (IC_{50} = 13.6 µg/mL), (11) (IC_{50} =12.1 µg/mL), (12) (IC_{50} =18.1 µg/mL) and (13) (IC_{50} =11.7 µg/mL) showed potent antioxidant activity.	Yan et al. 2019
Epicoccum nigrum MLY-3	*Bruguiear gymnorrhiza*	Furobenzotropolones B (2), 3-hydroxyepicoccone B (3), and compounds (5 and 8) with IC_{50} values ranging between 14.7 - 29.3 µM indicate promising DPPH antioxidant scavenging. Above compounds along with compound (7) exhibit efficient ABTS antioxidant scavenging.	Zou et al. 2021
Phomopsis sp. 33#	*Rhizophora stylosa*	Chromenopyridines derivatives (4) *(*IC_{50} = 34.0 µM*)* antioxidant cap*ability to scavenge DPPH radical.*	Chen et al. 2018
Aspergillus sp. xy02	*Xylocarpus moluccensis*	Phenolic bisabolane sesquiterpenoids analog compound (12) (IC_{50} =72.1 µM) has a minimal antioxidative scavenge DPPH radical activity.	Wang et al. 2018
Hypoxylon sp. Hsl2-6	*Bruguiera gymnorrhiza*	Diterpenoids and isocoumarin derivatives hypoxymarins (6) (IC_{50} = 15.36 ± 0.24 µM) and 5-hydroxysescandelin (11) (IC_{50} = 3.69 ± 0.07 µM) own DPPH scavenging antioxidant activity.	Hou et al. 2021

Table 1. Contd.

Mycosphaerella sp. SYSU-DZG01	*Bruguiera gymnorrhiza*	Compounds (1), 2-methoxycarbonyl-4,5,6-trihydroxy-3-methyl-benzaldehyde (4), 1,3-dihydro -5-methoxy-7-methylisobenzofuran (6) and epicoccolide B (8) (EC_{50} values range between 16.3 - 85.8 µM) reveal antioxidant activity by scavenging DPPH·	Qiu et al. 2019
Penicillium sp. MGP11	*Xylocarpus granatum*	New isocoumarin *penicimarin G* (8) (IC_{50} = 4.6 µM) has significant antioxidant activity.	Mei et al. 2021
Phoma sp. SYSU-SK-7.	*Kandelia candel*	Compound (7) (EC_{50} = 11.8 µM) possesses inhibition of radical scavenging activity as opposed to DPPH.	Chen et al. 2019
		Anti-acetylcholinesterase	
Cladosporium cladosporioides MA-299	*Bruguiera gymnorrhiza*	Polyketides ent-cladospolide F (3) (IC_{50} = 40.26 µM) potent enzymatic inhibition of AChE.	Zhang et al. 2019
Aspergillus sp. 16-5c	*Sterculia apetala*	Isoaustinol (3) (IC_{50} = 2.50 µM), dehydroaustin (7) (IC_{50} = 0.40 µM), and dehydroaustinol (8) (IC_{50} = 3.00 µM) showed AChEIs	Long et al. 2017
Aspergillus terreus H010	*Kandelia obovata*	1,2-dehydro-terredehydroaustin (1) (IC_{50} = 42.3 ± 0.20 µM) inactivates AChE enzyme.	Liu et al. 2018

Anticancer

Cancer or malignant is an abnormal growth of cells found either in organs or tissue of several types of ailments. It grows beyond the boundaries and spreads uncontrollably to other adjoining parts of the organs. It is the second supreme engender of mortality globally (approximately 9.6 million deaths in 2018). It ruined the lifestyle of humans physically, emotionally, and financially. Chemotherapy is a synthetic therapy applied to cure cancer that causes several side effects such as hair loss, fever, loss of appetite, diarrhea, fatigue, damage to lung tissue, heart problems, and kidney problems. Advance research in inventing anticancer drugs shows new and improved varieties of compounds derived from natural sources. Investigation of Taxol, a commercially anticancer drug that was procured from endophytic fungi *Taxomyces andreanae of Taxus brevifolia plant*, captivated the mycologists to explore the benefits of metabolites from diverse endophytic fungi (Bibi et al. 2020). The secondary metabolite components yielded by the endophytes have commercial importance towards humans as an anticancer drug. Mangrove plants place an active role in producing more novel phytochemical components, mainly due to the adaptable nature of the environment they survive. Mangrove plants are the storehouse of endophytes. The endophytes of mangrove plants have a symbiotic relationship that inherits the secondary metabolites from their host (Salini 2015). It produces metabolites for example, *Acanthus ilicifolius* mangrove store the endophyte *Diaporthe phaseolorum* SKS019 that produce metabolites deoxybostrycoidin (8) has cytotoxic activity that inhibits the cancer cell lines NCI-H460 (IC_{50} = 5.32 µM) and MDA-MB-435 (IC_{50} = 6.57 µM), and fusaristatin A (9) shows growth inhibition of cancer cell line MDA-MB-435 (IC_{50} = 8.15 µM) (Cui et al. 2017). *Xylocarpus granatum* mangrove plant has *Trichoderma* sp. Xy24 secretes 9R, 10R-dihydroharzianone (1) exhibit cytotoxic action that resists cell lines of MCF-7 (IC_{50} = 30.7 µmol/L) and HeLa. (IC_{50} = 30.1 µmol/L) (Zhang et al. 2016). *Penicillium*

chermesinum endophytes of *Hertiera littoralis* produce polyketide derivative compound (2-chloro-3,4,7-trihydroxy-9-methoxy-1-methyl-6H-benzo[c] chromen-6-one (1)) possess cytotoxicity opposing the cancer cell lines MOLT-3 (IC_{50} = 14.94 µM), HuCCA-1 (IC_{50} = 56.39µM), A-549 (IC_{50} = 115.71µM), and HepG2 (IC_{50} =55.06 µM) (Darsih et al. 2017). *Lasiodiplodia* sp. 318 from *Excoecaria agallocha* which generates lasiodiplodins 2,4-dihydroxy -6-nonylbenzoate (4) shows the most potent cytotoxicity resist of GH3 (IC_{50} =13.05 µM) and MMQ (IC_{50} =5.29 µM) cell lines (Huang et al. 2017).

Antimicrobial

Pathogenic microbes such as fungi, bacteria, and viruses can cause contiguous diseases that disseminate through different modes of transmission. It can be cured either by the administration of synthetic or herbal antimicrobial drugs. Synthetic drugs are well known for curing several communicable ailments but have high side effects on human health. Chronic uses of antibiotic drugs cause the influence of new multi-drug resistant microbes ongoing threats to the world. This threat urges an investigation of alternative sources of naturally available antimicrobial drugs. The discoveries of drugs from diverse natural sources (plants, animals, and non-pathogenic microbes) may have fewer side effects and more effective antimicrobial properties. Based on the proof of scientific research, mangrove endophytes render potential and notable robust sources of antimicrobial activities. Phytochemical compounds of mangrove endophytes can act as antimicrobial agents to cure communicable diseases (Kuzhalvaymani et al. 2020). *Penicillium citrinum* HL-5126 spotted from *Bruguiera sexangula var. rhynchopetala* produce benzopyran derivative compound (6) (MIC = 6.94 µg/mL) exhibit the most efficient inhibition of *Micrococcus tetragenus, Bacillus subtilis,* and *Bacillus cereus* (Zheng et al. 2016), *Penicillium* sp. GD6 spotted from *Bruguiera gymnorrhiza* has the metabolites 2-deoxy-sohirnone C (1) with MIC = 80 µg/ml that has an average resistance of Methicillin-resistant *Staphylococcus aureus (MRSA)* (Jiang et al. 2018). *Penicillium aculeatum* (No. 9EB) endophytes present in *Kandelia candel* has chromone metabolites derivative such as bacillisporin A (2) (MIC = 0.13 ± 0.02 µM), bacillisporin B (3) (MIC = 0.13 ± 0.02 µM) with significant antibacterial inhibition of *Bacillus subtilis*, whereas metabolite (1) known as (2′S*)-2-(2′-hydroxypropyl)-5-methyl-7, 8-dihydroxy-chromone, exhibit antibacterial activity oppose to *Salmonella* with a MIC = 2.00 ± 0.02 µM (Huang et al. 2017).

Antidiabetic

Diabetes is a chronic hyperglycemia disease that results from a disorder in insulin action and insulin secretion. It has common symptoms such as increased thirst, increased urinary discharge, ketonemia, and ketonuria. Diabetes is one of the globally occurring diseases, predicted to affect approximately a 693 million adults by 2045. Microvascular and macrovascular are the complications are provoked by diabetes. It causes several defects in the kidneys, nerves, eye, and cardiovascular, which elevates the mortality rate and ruin the

quality of life of diabetic patients. Alpha-glucosidase inhibitors treat type2 diabetic patients. The inhibitors slow down carbohydrates' absorption in the small intestine and mitigate the postprandial level of insulin and blood glucose (Van De Laar et al. 2005). Mangrove endophytic produce trove of metabolites that have inhibited α-glucosidase enzyme role, for example, *Alternaria* sp. SK6YW3L derived from mangrove plant *Sonneratia caseolaris* has a compound namely altenusin derivatives compounds (2) (IC_{50} = 78.2 μM), (3) (IC_{50} = 78.1 μM), and (9) (IC_{50} = 64.7 μM) exhibit medium α-glucosidase enzyme inhibition (Liu et al. 2016). *Sonneratia ovata* mangrove has an endophyte *Nectria sp. HN001* that contains a Nectriacids B (2) (IC_{50} = 23.5 μM) and C (3) (IC_{50} = 42.3 μM) indicate effective inhibitory activity toward α-glucosidase (Cui et al. 2016). *Penicillium aculeatum* (No. 9EB) identified from *Kandelia candel* produces compound (2) (IC_{50} = 33.55 ± 0.63 μM) and (3) (IC_{50} =95.81 ± 1.12 μM) possessed significant inhibitory activity against α-glucosidase (Huang et al. 2017).

Anti-inflammatory

Inflammation is the immune response to toxic stimuli involved in the wound healing process. Three prime pathways NF-ϰB, MAPK, and JAK-STAT, stimulate the inflammatory signal process. Any variance caused in these pathways might provoke inflammation-related diseases, including cancers, rheumatoid arthritis, type 2 diabetes, cardiovascular diseases, and atherosclerosis. Anti-inflammatory drugs impede the pathophysiological process of inflammation, thus reducing tissue damage and protecting patients from injuries. Therefore, it is impressive to mention that the availability of natural sources (plants and endophytic fungi) and bioactive components generated from them act as anti-inflammatory drugs. *Botryosphaeria* sp. SCSIO KcF6 identified from *Kandelia candel* can secrete a phenyl derivative (3) (IC_{50} = 1.12 μM), exhibited a specific cyclooxygenase-2 (COX-2) inhibitory activity (Ju et al. 2016). *Penicillium* sp. ZJ-SY2 endophytes from *Sonneratia apetala* produce metabolites peniphenone (1) and xanthones (3, 5, 7) (IC_{50} range between 5.9 - 9.3 μg/mL) owns an immunosuppressive activity (Liu et al. 2016). *Lasiodiplodia theobromae* ZJ-HQ1 endophytes from *Acanthus ilicifolius* produce metabolites lasiodiplactone A (1) (IC_{50} = 23.5 μM) signify anti-inflammatory property by precluding the nitric oxide (NO) generation in lipopolysaccharide (LPS) promoted RAW264.7 cells (Chen et al. 2017).

Antioxidant

Any disproportion between the production of reactive oxygen species (ROS) and antioxidants induces oxidative stress, which damages the tissue. Free radicals are highly reactive and unstable molecules generated in the body either by the normal metabolic process of cells as a by-product of oxidation or by exposure to carcinogens in our environment (smoke, air pollution, some viruses, chemical exposure, ultraviolet radiation, and medical radiation). Cells get damaged by antioxidant deficiency that engenders more accumulation of

free radicals, leading to various kinds of ailments such as cancer, asthma, diabetes, atherosclerosis, and many others. An antioxidant is a compound available in diverse forms (natural or artificial) that inhibits or delays the accumulation of free radicals (Pizzino et al. 2017). Phenolic compounds present in the endophytes were the primary sponsor of the antioxidant properties. *Cladosporium sp. OUCMDZ-302* endophytes are spotted from *Excoecaria agallocha* has an antioxidant activity of secondary metabolite polyketide compounds (4) (IC_{50} = 2.65 µM), (8) (IC_{50} = 0.24 µM), (9) (IC_{50} = 5.66 µM) and (10) (IC_{50} = 6.67 µM) showed promising DPPH antioxidant scavenging (Wang et al. 2018). *Ascomycota* sp. SK2YWS-L obtained from *Kandelia candel* produces an antioxidant metabolite ascomindones A (1) (IC_{50} = 18.1 µM) possesses efficient scavenging activities that inhibit DPPH (Tan et al. 2016).

Anti-Acetylcholinesterase

Acetylcholinesterase (AChE) is the prime enzyme of the cholinergic nervous system. Predominant in the neuromuscular junctions and cholinergic synapses. AChE ceases neurotransmission at cholinergic synapses by rapid hydrolysis of acetylcholine to choline and acetate this enzyme activity is inhibited by Acetylcholinesterase inhibitors (AChEIs), which in turn augment the accumulation of acetylcholine in neuromuscular junctions, central nervous system, and autonomic ganglia, where acetylcholine receptors are surplus (Cheung et al. 2012). Hence, AChEIs treat dementia with Lewy body, Parkinson's, and Alzheimer's diseases. Plants are considered a most efficient and enormous source for AChEIs enzyme but, microbes' production of these enzymes indicates an eco-friendly, cost-effective, efficient, and alternative approach easily manipulated (Zhang et al. 2019). *Kandelia candel* is a mangrove plant that stores a plethora of endophytes one of them is *Penicillium* sp. SK5GW1L which has *a*-pyrone meroterpenoids compounds (3) (IC_{50} = 3.03 µM), (4) (IC_{50} = 0.23 µM) and (5) (IC_{50} = 0.028 µM) shows sturdy inhibition of acetylcholinesterase (AchE) (Ding et al. 2016). Liu et al. (2018), reported that compounds 1,2-dehydro-terredehydroaustin (1) (IC_{50} = 42.3 ± 0.20 nM) resist the AChE enzyme produced by *Aspergillus terreus* H010 endophytes of *Kandelia obovata* mangrove plants.

CONCLUSION

This review accentuates that mangrove endophytic fungi of SCS has more capacity to generate an impressive range of metabolites. The plant-endophyte symbiotic concomitant activates the production of bioactive components likely alkaloid, depsipeptides, terpenes, lactones, allenolic, cyclic peptides, quinone, chinone or terpenoid, flavonoid, phenolic acid, steroid, with propitious biopharmaceutical potential including anticancer, antimicrobial, antioxidant, anti-inflammatory and antidiabetic. Out of 84 mangrove species recorded currently, only 27 of them have been pharmacologically corroborated in terms of endophytic fungi. Still, there is a meager of knowledge that insists more investigation is needed to explore the relationship and mechanism of

association between the endophytic fungi and host in order to procure enormous metabolites that have a significant role in medical field.

AUTHORS CONTRIBUTION

All authors reviewed the literature and compilation of this manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors would like to acknowledge support from Universiti Brunei Darussalam. Grant No. UBD/RSCH/1.4/FICBF(b)/2020/030 'Mangrove endophytes - study of plant host interactions, bioactive compounds and their applications'. MMN is grateful to Universiti Brunei Darussalam for the UBD Bursary Award (UBA) Scholarship.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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