Bioactive Metabolites of Endophytic fungi of *Avicennia marina* (Forssk.) Vierh.

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ABSTRACT

Endophytic fungi are microorganisms residing within the plant without causing any harm to the host plants. These fungi are known to produce diverse classes of chemical compounds with useful biological activities. *Avicennia marina* (Forssk.) Vierh. is a mangrove plant belonging to family *Acanthaceae* and used in traditional medicine. Mangrove plant *A. marina* harbors a large number of endophytic fungi which are known to produce an array of biologically active heterocyclic compounds. In the present review nearly 135 compounds reported from the endophytic fungi associated with mangrove plant *A. marina* are highlighted. These compounds were isolated from the species of genera *Xylaria, Aspergillus, Penicillium, Stemphylium, Cladosporium, Phoma*, and an unidentified fungus.

Keywords: Endophytic fungi, *Avicennia marina*, bio-active compounds, *Xylaria, Penicillium*

INTRODUCTION

Endophytic fungi are microorganisms residing within the plants without causing any harm to the host. These fungi are known to produce a range of chemically diverse compounds with a number of biological activities. *Avicennia marina* (Forssk.) Vierh. is a mangrove plant belonging to family *Acanthaceae* and used in traditional medicine which harbors a large number of endophytic fungi is known to produce a diverse class of heterocyclic compounds. Mangrove associated endophytic fungi are the source of various metabolites belonging to class anthraquiones, cyclic peptides, diketopiperazine, esters, isocoumarin, lactones, sesquiterpene, steroids, xanthones, and sphingolipids, xyloketals, xyloallenolides (Zhu et al., 2009; Deshmukh et al., 2015, 2018, 2020) with various biological activities such as antibacterial, antifungal, anticancer, anti-inflammatory, antioxidant, anti-angiogenesis activity, etc. In this review, we have highlighted nearly 135 compounds that are reported from species of genera *Xylaria, Aspergillus, Penicillium, Stemphylium, Cladosporium, Phoma*, and an unidentified fungus associated with *A. marina* (Fig. 1). The details such as location of collection of host, isolated metabolites and their biological properties are presented in table 1.

The genus *Avicennia* L. has five species including *A. alba* Bl., *A. integra* N.C. Duke, *A. marina*, *A. officinalis* L. and *A. rumphiana* Hallier f. and they all grow in mangroves. Among the different mangrove plant genera, *Avicennia* is the most widely distributed in the mangroves around the world (Duke, 1991). Further, from the different species in *Avicennia*, the plant species *A. marina* is most widely distributed (Tomlinson, 1986). *A. marina* is a shrub or a tree growing up to 14 meters. Three sub species of *A. marina* have been accepted including *A. marina* subsp. *australasica, A. marina* subsp. *eucalyptifolia* and *A. marina* subsp. *marina* but their distribution is less observed (Duke, 1991). Among the three oceanic regions, *A. marina* is more widely distributed in the mangrove forests of Indian ocean region (Abdel-Wahab et al., 2020). A recent review on *A. marina* shows that on this plant alone, 149 species of marine fungi have been identified (Abdel-Wahab et al., 2020). Marine fungi are those that colonize the submerged parts of plant substrata in marine environments. The number 149 is exclusive of fungi that occur on the aerial parts of this plant. Of the 149 marine fungi identified from this host, 26 fungi were recorded only from this host (host specific) including 23 as new fungi. Since many of them are new; the host specificity may not be attributed as of now (Abdel-Wahab et al., 2020). Out of the 149 marine fungi reported from *A. marina*, only 14 marine fungal species have been investigated for their secondary metabolites. These marine fungi are known to produce novel compounds.
bioactive compounds which possess antimicrobial, cytotoxic, phytotoxic, antimalarial and anti-diabetic properties (Abdel-Wahab et al., 2020).

Studies on the endophytic fungal diversity in mangrove plants has gained much attention recently. Kumaresan and Suryanarayanan (2001) investigated the endophytic fungi of seven different mangrove plants in Pichavaram mangroves, Tamil Nadu, East coast of India and out of this A. marina yielded 18 fungal taxa including four sterile mycelia. A Phoma sp. is the most dominant on this host plant. Recently, the world-list of endophytic fungi has been reviewed by Rashmi et al. (2019) and they found 2770 species belonging to 877 genera. Among these Penicillium, Alternaria, Fusarium, Colletotrichum, Aspergillus and Xylaria in that order to be the most speciose genera. Some of these genera are also commonly found as endophytes on A. marina, belonging to Xylaria, Penicillium and Aspergillus, and most of the bioactive compounds reported from them. The fact that these few genera from A. marina have produced approximately 135 secondary metabolites indicates that these genera appear to be highly adaptable to all kinds of harsh-conditions and can outcompete other fungal or bacterial species in addition to protecting the host from pathogens. In bio-activity evaluation, these metabolites have shown useful pharmacological properties. Some metabolites have good potential to act as leads for the development of novel bioactive molecules with drug-like properties. In the present review, the reported bioactive metabolites from A. marina are discussed based on their source organisms, origin and biological properties. The summary of the bioactive metabolites and their sources are presented in Table 1 and their classification based on chemical nature is highlighted in Table 2.

**COMPOUNDS ISOLATED FROM XYLARIA SP.**

Five unique metabolites, xyloketals A-I (1-9), and a known compound (10) (Fig. 2) were isolated from mangrove fungus Xylaria sp. (no. 2508), obtained from the seeds of A. marina in Mai Po, Hong Kong. (Lin et al. 2001a; b; Liu et al.; 2006; Yin et al., 2008). Xyloketal A (1) displayed the acetylcholine esterase inhibitory activity at 1.5 × 10⁻⁷ mol/L (p <0.01) (Lin et al., 2001a). The xyloketalas A (1), B (2), and F (6) displayed L-calcium channel blocking activities with inhibiting rates observed as 21.47%, 12.05%, and 50.33%, respectively at the concentration of 0.03 µM (Wu et al., 2005a). Xyloketal B (2) has been implicated in the treatment for hypoxic-ischemic brain injury (Xiao et al., 2015). It also exhibited a potential for the treatment of glioblastoma which is one of the aggressive types of brain tumors (Chen et al., 2015).

Three aromatic allenic ethers xyloallenolide (11), but-2,3-dienyl ether of p-hydroxycinnamic acid (12) and eucalyptene (13) (Lin et al., 2001b), and three new metabolites, named xyloester a (14), and xyloallenolide b (15), xyloketal j (16), together with a known substituted dihydrobenzofuran (17) (Fig. 2) were reported (Xu et al., 2008). A novel metabolite xylopyridine A (18) and a known compound pyrocoll (19) (Xu et al., 2009), and xyloallenolide A (20) (Fig. 3), was purified from Xylaria sp. (2508) (Lu et al., 2012). Compound (18) showed a strong DNA-binding affinity toward calf thymus (CT) DNA presumably via an intercalation mechanism; thus, it is exploitable as a strong DNA-binder (Xu et al., 2009). Compound xyloallenolide A (20) induced angiogenesis in zebrafish embryos and in human endothelial cells, which was accompanied by increased phosphorylation of eNOS and Akt and NO release. Inhibition of PI3K/Akt/eNOS by LY294002 or L-NAME suppressed X-13-induced angiogenesis (Lu et al., 2012).

**COMPOUNDS ISOLATED FROM PENICILLIUM SP.**

New polyoxygenated dihydropyrano [2,3-c]pyrrole-4, 5-dione derivative called pyranonigrin F (21), together with previously isolated analog, pyranonigrin A (22) (Fig. 3), were purified from Penicillium brocae MA-231, an endophytic fungus residing inside the A. marina. Compounds (21 and 22) exhibited potent antibacterial activity against Staphylococcus aureus and aqua-bacteria Vibrio harveyi and V. parahaemolyticus with MIC values of 0.5 mg/mL, for each strain and interestingly, appeared better than the positive control chloromycetin (with MICs 8.0, 2.0, and 128.0 mg/mL, respectively). Compounds (21 and 22) also exhibited good activity against plant pathogens Alternaria brassicae.
### Table 1. Novel bioactive compounds reported from endophytic fungi associated with *Avicennia marina*.

<table>
<thead>
<tr>
<th>No.</th>
<th>Strain</th>
<th>Site of Collection</th>
<th>Compounds Isolated</th>
<th>Biological Target</th>
<th>Biological active value (IC_{50}/ED_{50})</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Aspergillus</em> sp.</td>
<td>No. (no. 2508)</td>
<td>Xyloallene A, 14, Xyloallene B, 15, Xyloallene C</td>
<td>Strong DNA-binding affinity toward calf thymus (CT) DNA presumably via an intercalation mechanism, thus it is exploitable as a strong DNA intercalator</td>
<td>MIC 16.0 µg/mL</td>
<td>Lu et al., 2009</td>
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<td>2.</td>
<td><em>Aspergillus</em> sp.</td>
<td>No. (no. 2508)</td>
<td>Xyloallene A (14), Xyloallene B (15), Xyloallene C (16), Xyloallene D (17), Xyloallene E (18), Xyloallene F (19)</td>
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**Note:** The table continues with further entries, including other fungal strains, compounds isolated, biological targets, and references. The content has been truncated for brevity, as the full table would be extensive and not easily readable in this format.
and Colletotrichum gloeosporioides with MICs of 0.5 mg/mL, which was better than positive control bleomycin (with MICs 32.0 and 4.0 mg/mL, respectively) (Meng et al., 2015a).

Five new sulfide diketopiperazine derivatives, namely, penicibocarazines A–E (23–27) (Fig. 3), along with previously isolated congener phomazine B (28) (Fig. 4), were purified from Penicillium brocæ MA-231. Compounds (24–26 and 28) displayed antibacterial activity against Staphylococcus aureus, with MIC values of 32.0, 0.25, 8.0, and 0.25 μg/mL.
respectively, (positive control, chloromycetin, MIC = 4.0 μg/mL). Compound (25) also showed activity against Micrococcus luteus with MIC value of 0.25 μg/mL, which was better than that of the positive control, chloromycetin (MIC = 2.0 μg/mL). In addition, compounds (24, 26, 27 and 28) displayed activity against plant pathogen Gaumannomyces graminis with MIC values of 0.25, 8.0, 0.25, and 64.0 μg/mL, respectively, (positive control amphotericin B, MIC = 16.0 μg/mL) (Meng et al., 2015b).

Six new disulfide-bridged diketopiperazine derivatives, brocazines A-F (29-34), together with previously isolated analog epicorazine A (35) (Fig. 4), were purified from Penicillium brocae MA-231. Compounds (29, 30, 33 and 34) exhibited cytotoxicity with IC50 values ranging from 0.89 to 9.0 μM against the Du145, HeLa, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, and U251 cell lines. Compounds (29 and 30) exhibited good activity against the SW480 cells, with IC50 values of 2.0 and 1.2 μM, respectively. Compound (34) displayed potent activity against the Du145 and NCI-H460 cells, with IC50 values of 1.7 and 0.89 μM, respectively (Meng et al., 2014).

Four new thiodiketopiperazine alkaloids, penicicrozones F-I (36-39), along with two new nitrogen-containing p-hydroxyphenopyrrozin derivatives brocapyrrozins A and B (40-41) as well as six known alkaloids epicoccin A (42), phomazine A (43), 4-hydroxy-3-phenyl-1H-pyrrol2(5H)-one (44), hexahydro-2-hydroxy-1-phenyl-1H-pyrrolizin-3-one (45), phenopyrrozine (46) (Fig. 4), and p-hydroxyphenopyrrozine (47) (Fig. 5), were purified from mangrove-derived endophytic fungus P. brocae MA-231 using OSMAC (one strain-many compounds) method. Compounds (40 and 44) exhibited good antibacterial activity against S. aureus with MIC values of 0.125 and 0.5 μg/mL, respectively (positive control, chloromycetin, MIC = 0.5 μg/mL). While compounds (38 and 39) displayed activity against E. harveyi with MIC values of 16.0 and 32.0 μg/mL, respectively, (positive control chloromycetin, MIC = 4 μg/mL). Compound (38) also displayed antibacterial activity against Escherichia coli, Aeromonas hydrophilia and Vibrio parahaemolyticus with MIC values of 16.0, 32.0, and 16.0 μg/mL, respectively, (positive control chloromycetin, MIC = 2.0, 4.0, 2.0 μg/mL). Compounds (40, 44 and 41) exhibited good antifungal activity against Fusarium oxysporum MIC values of 0.25, 0.125 and 64.0 μg/mL respectively, while positive control zeocin exhibited antifungal activity with MIC value of 0.5 μg/mL (Meng et al., 2017).

Four new diketopiperazines including spirobrocazines A-C (48-50) and brocazine G (51) (Fig. 5), were purified from Penicillium brocae MA-231 using the one strain many compounds (OSMAC) approach. Compound (51) displayed potent cytotoxic activity against A2780 and 2780 CisR cell lines, with IC50 values of 6.64 and 6.61 μM, respectively, which was found better than cisplatin (positive control) with IC50 value of 1.67 and 12.63 μM, respectively. In addition,

Fig. 3. Bio-actives reported from Xylaria sp. (18-20) and Penicillium sp. (21-35) an endophyte from A. marina.

Fig. 4. Bio-actives reported from Penicillium sp. (36-52) an endophyte from A. marina.
Compound (51) also exhibited good antibacterial activity against S. aureus with MIC value of 0.25 μg/mL, while positive control, chloromycetin displayed antibacterial activity with MIC, values of 0.5 μg/mL. Compound (48) exhibited moderate activity with MIC values of 32.0, 16.0, and 64.0 μg/mL against E. coli, S. aureus, and V. harveyi, respectively while chloromycetin as positive control showed MIC values of 2.0, 0.5, and 2.0 μg/mL, respectively. Compound (50) also exhibited activity against E. coli, Aeromonas hydrophilia, and V. harveyi, each with an MIC value of 32.0 μg/mL. (Meng et al., 2016).

A new aurone glycoside, (Z)-7,4’-dimethoxy-6-hydroxy-aurone-4-O-β-glucopyranoside (DHAG) (Fig. 5), was isolated from Penicillium sp.FJ-1, an endophyte associated with mangrove plant A. marina. Compound (52) displayed potent antifungal activity against Candida sp., comparable to that of amphotericin B and appeared better than fluconazole and also inhibited extracellular phospholipase secretion in a concentration-dependent manner (Song et al., 2015).

Two new compounds, named (Z)-7,4’-dimethoxy-6-hydroxy-aurone-4-O-β-glucopyranoside (DHAG) (52) and (−)-4-O-(4-O-β-D-glucopyranosylcaffeoyl) quinic acid (53) (Fig. 5), were isolated from the endophytic fungus Penicillium citrinum of mangrove plant A. marina. Compound (53), exhibited potent chemoreversal activity, mainly by inhibiting P-glycoprotein efflux pump function (Liu et al., 2015a). It is reported that DHAG (52) increased the viability of PC12 cells, attenuated the imbalance of redox, and decreased cellular apoptosis in an H2O2-induced oxidative stress model. Furthermore, treatment with DHAG could markedly attenuate the anxiety-like behavior of rats induced by DOX. It is demonstrated that DHAG can be developed as a neuroprotective agent. (Li et al., 2019).

Compound (55), displayed activity against Tca8113, MG-63 and WRL-68 cells with an IC50 value of 10 μM, 55 μM and 58 μM, respectively. In nuce mice model, compound (55) displayed noteworthy inhibition of tumor growth of human osteosarcoma. Compound (54), displayed weak activity with IC50 values of 26 and 35 μM, against Tca8113 and MG-63 cells, respectively. Positive control taxol, displayed cytotoxicity against Tca8113 and MG-63 cell lines with IC50 values of 46 and 10 nM, respectively (Zheng et al., 2014).

Compounds (10R,14R)-10-Hydroxydihydroresorcylide (56), brocaketone A (57) and brocaketone D (58) (Fig. 5), were purified from P. broc ae MA-192, residing inside the leaves of A. marina, a mangrove plant, collected from Hainan Island, China. Compounds (56-58) displayed potent antioxidant activity in DPPH assay with IC50 values of 14.4, 5.9, and 16.3 μg/mL, respectively, while positive control BHT displayed scavenging activity with IC50 value of 18.5 μg/mL (Zhang et al., 2015).

**COMPOUNDS ISOLATED FROM ASPERGILLUS**

A new a-pyrone derivative, Allantopyrone E (59) was purified from fungal endophyte A. versicolor associated with the fruit of the mangrove plant A. marina obtained from Port Safaga, Red Sea Governorate, Egypt. Allantopyrone E (59) displayed cytotoxic activity against HeLa cells with IC50 value of 50.97 μM (Elsbaey et al., 2020).
Eight new α-pyrones, nigerapryrones A-B (60, 61), (Fig. 5), C-E (62-64) and nigerapryrones F-H (65-67), together with previously reported congeners, nisipyriones B (68) and A (69) (Fig. 6), were purified from endophytic fungus Aspergillus niger MA-132, residing inside the mangrove plant Aspergillus marina. Compound (64), displayed cytotoxic activity against SW1990, MDA-MB-231, A549, MCF-7, HepG2, DU145, NCI-H460, and MDA-MB-231 cell lines with IC_{50} values of 38, 48, 43, 105, 86, 43, and 48 μM, respectively. Positive control, fluorouracil displayed cytotoxicity against A549, HepG2, DU145, MCF-7, SW1990, NCI-H460, and MDA-MB-231 cell lines, with IC_{50} values of 52, 109, 3.3, 31, 121, 8.5, and 59 μM, respectively. Compound (61), was found selectively active against HepG2 cell line with an IC_{50} of 62 μM while compound (69) exhibited activity against the A549 cell line with an IC_{50} of 62 μM, and nigerapryrone D (63) showed average or poor activity against the MCF-7, HepG2, and A549 cell lines, with IC_{50} values of 121, 81, and 81 μM, respectively (Liu et al., 2011). Two novel sterols, nigerasterols A (70) and B (71), along with already reported cyclopentapeptides, malformins A1 (72) and C (73) (Fig. 6), were purified from Aspergillus niger MA-132, residing inside the mangrove plant Aspergillus marina. Compounds (70 and 71) displayed potent cytotoxic activity against HL60 cell line IC_{50} values of 0.30 and 1.50 μM, and against A549 cell line with IC_{50} values of 1.82 and 5.41 μM, respectively.

Compounds (72 and 73) displayed poor activity against Staphylococcus aureus with 9.0 and 8.5 mm diameter of clear zone on inhibition, respectively at a concentration of 20 mg/disk, while positive control chloramphenicol inhibited S. aureus with clear zone of inhibition of 20.0 mm at the same concentration (Liu et al., 2013).

Two new oxindolo diterpene epimers, anthcolorin G (74) and anthcolorin H (75), nine new meroterpenes, (7R,8R)-8-hydroxysydowic acid (76), (7S,10S)-10-hydroxy-sydowic acid (77), (7S,11R)-12-hydroxy-sydowic acid (78), (7S,8R)-12-acetoxy-sydowic acid (79), (7R,8R)-1,8-epoxy-11-hydroxy-sydonic acid (80), 7-deoxy-7,14-didehydro-11-hydroxy-sydonic acid (81), 7-deoxy-7,14-didehydro-12-acetoxy-sydonic acid (82) (Fig. 6), and (E)-7-deoxy-7,8-didehydro-12-acetoxy-sydonic acid (83), (7R)-11-hydroxy-sydonic acid methyl ester (84), and a benzoic acid derivative, 3-hydroxy-4-(1-oxo-ethane)-benzoic acid (85), in addition to twelve known compounds (Sydowic acid (86), (7R,10R)-iso-10-hydroxy-sydowic acid (87), engyodontiumone J (88), engyodontiumone I (89), (E)-7-deoxy-7,8-didehydro-12-hydroxy-sydonic acid (90), (7R)-11-hydroxy-sydonic acid (91), an epimeric mixture of (7R,11R) and (7R,11S)-12-acetoxy-sydonic acid (92), 12-acetoxy-1-deoxy-sydonic (93), dioxinolone (94), macrosporin (95), and ergosteryl peroxide (96) (Fig. 7), were purified from endophytic fungus Aspergillus versicolor isolated from mangrove plant Aspergillus marina and grown on the solid rice culture. The site of collection was 17 K Safaga, Red Sea, Egypt.
Compounds (75, 82, 83 and 94), were found active with IC\textsubscript{50} values of 43.7, 83.8, 53.5, 83.8 \mu M, respectively against Hela cell lines (Elbaey et al., 2019).

**COMPONDS ISOLATED FROM OTHER ENDOPHYTIC FUNGI**

Two new anthraquinones, altersolanol Q (97) and 10-methylaltersolanol Q (98), and the new dimer alterporriol X (99), along with 13 known analogs dihydroaltersolanol B (100) and C (101) (Fig.7), altersolanol A (102), B (103), and N (104), 1-hydroxy-3-methoxy-6-methylanthraquinone (105), macrosporin (95), altechromone A (106), alterporriol D (107), E (108), R (109), V (110), and W (111) (Fig. 8), were extracted from endophytic fungus S. globuliferum grown on white bean solid culture media. S. globuliferum, was purified from the Egyptian mangrove plant A. marina (Moussa et al., 2016). Compounds (101-103 and 108) were found active against L5178Y cell lines with IC\textsubscript{50} values of 3.4, 2.53, 3.78, and 6.9 \mu M, respectively (Debbab et al., 2009; Liu et al., 2015b). Compound (104) also exhibited potent cytotoxicity against L5178Y cells with IC\textsubscript{50} values in the low micro-molar range (Debbab et al., 2012). Mishra et al. (2015) reported that Compound (102) displayed potent cytotoxicity against 34 human cancer cell lines in vitro, with mean IC\textsubscript{50} values of 0.005 \mu g/mL (Mishra et al., 2015).

Five novel 12-membered macrolides containing thioketals, thiocladosalopidides F-J (112-116), along with previously isolated analogues, pandangolide 3 (117), thiocladosalopid A (118), seco-secopatulolide C (119), and iso-cladosalopid B (120) (Fig. 8), were isolated from endophytic fungus Cladosporium oxysporum associated with the root of mangrove plant A. marina collected from Hainan Province, China. Compounds (112-120) displayed antibacterial activity with MIC values ranging from 4 to 32 \mu g/mL against Edwardsiella tarda and E. ictarada, the aquatic pathogens. Compound (113) exhibited potent activity against E. tarda with MIC values of 4 \mu g/mL and compound (120) was found active against plant pathogenic fungus Cytospora mandshurica with MIC values of 8 \mu g/mL (Wang et al., 2020).

A new lactone, 1,8-dihydroxy-10-methoxy-3-methylidendrobenzo[b,e]oxepine-xanthen-9-one (121), and two new xanthones, 1-hydroxy-8-(hydroxymethyl)-6-methoxy-3-methyl-9H-xanthen-9-one (122) and 1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-methyl-9H-xanthen-9-one (123) (Fig. 9) were purified from Phoma sp. SK3RW1M residing inside the roots of A. marina. The site of collection was Shankou mangrove, Guangxi, China. Compounds (121-123) were inactive when tested for cytotoxic properties (Pan et al., 2010).

Two new metabolites, the cyclo-(L-Phe-L-Leu1-L-Leu2-L-Leu3-L-Ile) (124) and (3S,4R)-dihydroxy-(6S)-supercucumulopyranone (125) (Fig. 3) were purified from endophytic fungus number 2524 residing inside the seed of A. marina collected from Hong Kong. Both the compounds displayed poor activity against Bel-7402, NCI-4460 cancer cell line and 0.005 \mu g/mL (Mishra et al., 2015). Two new metabolites, namely 2106 A (126) and cyclo-(N-MeVal-N-MeAla) (127) (Fig. 3) were obtained from endophytic fungus number 2106 isolated from the seeds of the mangrove A. marina in Hong Kong. No activity is reported for both the compounds (Wang et al., 2008).

A known farinomalein derivative Farinomalein (128) along
AN OVERVIEW AND CONCLUSION AND FUTURE PROSPECTS

In the present study, we have reported 135 compounds from mangrove plant *A. marina* with various biological activities (antibacterial, antifungal, anticancer, anti-inflammatory, antioxidant, anti-angiogenesis, and L-calcium channel blocker activity). These compounds belong to the various chemical classes such as anthraquinone, piperazine, glycoside, cyclopeptides, sterol, ergostrol, xanthone, macroline, etc. (Table 2). Some of the isolated compounds, viz. (Z)-7,4′-dimethoxy-6-hydroxy–aurone-4-O-β-glucopyranoside (DHAG) (52) with potent anti-inflammatory, altersolanol A (102) with anticancer, and Xyloketal B (2) with neuroprotective activity can be potential drug candidates. In this review we found majority of the compounds were isolated from the endophytic fungal genera *Xylaria, Aspergillus, Penicillium, Stemphylium, Cladosporium, Phoma* and an Unidentified fungus. It is also found that only a few compounds were screened for biological activity due to insufficient quantity, hence there is a need to produce the compounds in sufficient quantities and to evaluate these compounds in various screening activities using high throughput screening.

The methods like OSMAC, Co-cultivation can help in exploring chemical diversity. The application of epigenetic modifiers in culture media will help in expressing the biosynthetic gene clusters (BGC), responsible for unexpressed bioactive metabolites hence increasing chemical diversity. Next-generation sequencing (NGS) data in combination with other bioinformatics tools will help in generating chemical diversity. Around a dozen secondary metabolites were reported from 14 fungal species out of 149 marine fungi screened for secondary metabolites from mangrove plant *A. marina* (Abdel-Wahab et al., 2020). It is advisable to explore the fungal diversity from different locations for bioactive metabolites as the factors like salinity, temperature, the maturity of the mangrove site, availability of decaying materials inside the mangroves, associated mangrove and terrestrial trees, tidal amplitude, and other factors account for this. The fact that typical marine fungi grow slowly, and their maintenance is difficult and hence many of them are not screened for bioactives, made mycologists to look for the isolation of endophytic fungi which are relatively easier to isolate and maintain, are the ones screened more for bioactive compounds.

*Mangrove plant A. marina* is used in various traditional and folk medicines and is known to produce diverse chemical compounds (El Dohaji et al., 2020). The endophytes and other marine fungi associated with this plant can be a potential source of bioactive metabolites and should be the prime target in the exploration of new drugs due to their application in the pharmaceutical industry.

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