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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 anthraquinones, 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

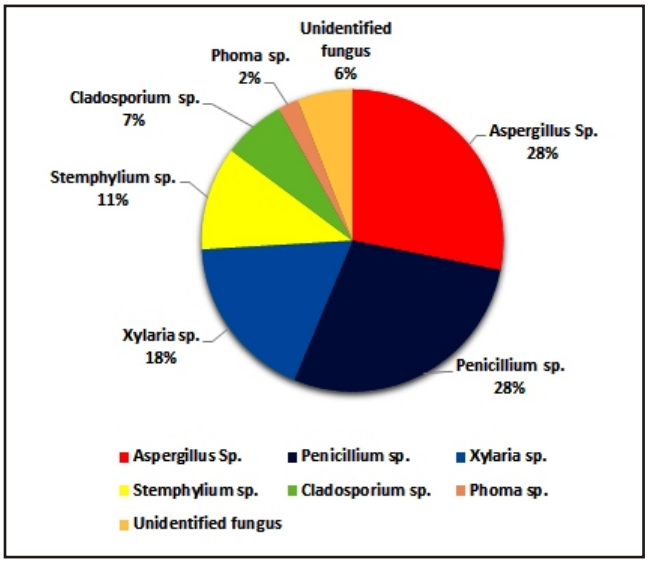

Fig. 1. Percentage distribution of bio-actives reported from various endophytic fungi of *A. Marina*

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

bioactive compounds which possess antimicrobial, cytotoxic, phytotoxic, antimalarial and antidiabetic 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; Wu *et al*. 2005a; b; Liu *et al*.; 2006; Yin *et al*., 2008). Xyloketal A (**1**) displayed the acetylcholine esterase inhibitory activity at 1.5×10^{-6} mol/L ($p < 0.01$) (Lin *et al*., 2001a). The xyloketals 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

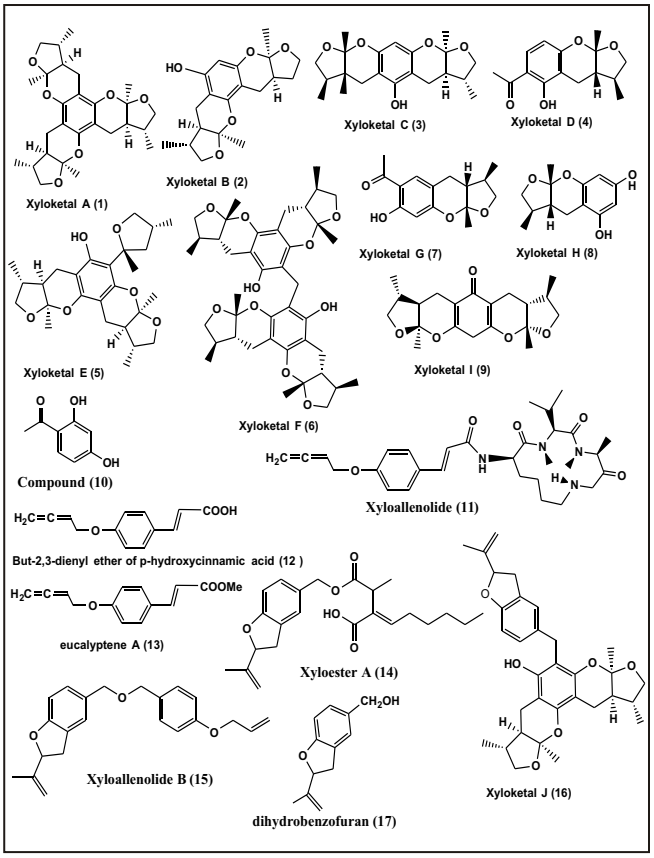

Fig. 2. Bio-actives reported from *Xylaria* sp. an endophyte from *A. marina* (1-17)**.**

xylopyridine A (**18**) and a known compound pyrocoll (**19**) (Xu *et al*., 2009), and xyloallenoide 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 xyloallenoide 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 *Staphyllococcus 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*.

Sr. No.	Fungal strain	Site of Collection	Compounds Isolated	Biological target	Biological active value (IC_{50}/ED_{50})	Reference
1.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal A (**1**),	acetylcholine esterase.	1.5 × 10-6 mol/L	Lin *et al*., 2001a
2.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal B (**2**),			Lin *et al*., 2001a
3.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal C (**3**),			Lin *et al*., 2001a
4.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal D (**4**),			Lin *et al*., 2001a
5.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal E **(5),**			Lin *et al*., 2001a
6.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal F **(6),** xyloketals A **(1)**, B **(2)**	L-calcium channel blocking activity	Inhibition rates were 21.47%, 12.05%, and 50.33% at 0.03 μM/L concentration	Wu *et al*. ,2005a
7.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	xyloketal G **(7),**			Wu *et al*. ,2005 b
8.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal H **(8),**			Liu *et al*., 2006, Yin *et al*., 2008
9.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloketal I **(9)**			
10.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Compound (**10**)			Lin *et al*., 2001a
11.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloallenolide (**11**) But-2,3-dienyl ether of p-hydroxycinnamic acid (**12**) and Eucalyptene (**13**)			Lin *et al*., 2001b
12.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloester A (**14**), Xyloallenolide B (**15**), Xyloketal J (**16**), Dihydrobenzofuran (**17**)			Xu *et al*., 2008
13.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xylopyridine A **(18),**	Strong DNA-binding affinity toward calf thymus (CT) DNA presumably via an intercalation mechanism, thus it is exploitable as a strong DNA-binders		Xu *et al*., 2009
			Pyrocoll (**19**),			
14.	*Xylaria* sp. (no. 2508)	Mai Po, Hong Kong	Xyloallenoide A **(20)**,	Inhibition of PI3K/Akt/eNOS by LY294002	Induces angiogenesis in zebra fish embryos and in human endothelial cells	Lu *et al*., 2012
15.	*Penicillium brocae* MA-231		Pyranonigrin F (**21**), Pyranonigrin A (**22**)	*S. aureus* and aqua-bacteria *Vibrio harveyi* and *V. parahaemolyticus*	MIC, 0.5 μg/mL each	Meng *et al*., 2015a
			Positive control chloromycetin		MICs 8.0, 2.0, and 128.0 μg/mL)	
			Pyranonigrin F (**21**), Pyranonigrin A (**22**)	*Alternaria brassicae* and *Colletotrichum gloeosprioides*	MICs, 0.5 μg/ mL for each strain	
			Positive control bleomycin		MICs 32.0 and 4.0 μg/mL,	
16.	*Penicillium brocae* MA-231		Penicibrocazines A (**23**)			Meng *et al*., 2015b
			Penicibrocazines B-D (**24-26**), Phomazine B (**28**),	*Staphylococcus aureus*,	MIC, 32.0, 0.25, 8.0, and 0.25 μg/mL.	
			Positive control, chloromycetin		MIC, 4.0 μg/mL	
			Penicibrocazine C (**25**)	*Micrococcus luteus*	MIC, 0.25 μg/mL,	
			Positive control, chloromycetin		MIC, 2.0 μg/mL	
			Penicibrocazines B (**24**), Penicibrocazines D (**26**), Penicibrocazines E (**27**), Phomazine B (**28**),	*Gaeumannomyces graminis*	MIC, 0.25, 8.0, 0.25, and 64.0 μg/mL	
			Positive control amphotericin B		MIC, 16.0 μg/mL	
17.	*Penicillium brocae* MA-231		Brocazines A, B, E, F (**29, 30, 33, 34**),	Du145, HeLa, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, and U251 cell lines	IC_{50} values ranging from 0.89 to 9.0 μM.	Meng *et al*., 2014
18.	*Penicillium brocae* MA-231		Brocazines A, B (**29, 30**),	SW480 tumor cell line	IC_{50}, 2.0 and 1.2 μM	
			Brocazines F (**34**)	DU145 and NCI-H460 cell lines,	IC_{50} 1.7 and 0.89 μM,	
			Brocazines C-D (**31, 32**), Epicorazine A (**35**)	-	-	
19.	*Penicillium brocae* MA-231		Penicibrocazines F-G (**36-37**), Epicoccin A (**42**), Phomazine A (**43**), Hexahydro-2-hydroxy-1-phenyl-1H- pyrrolizin -3-one (**45**), Phenopyrrozine (**46**), and p-hydroxyphenopyrrozin (**47**)			Meng *et al*. ,2017
			Brocapyrrozins A (**40**), 4-Hydroxy-3-phenyl-1H-pyrrol2(5H)-one (**44**),	*S. aureus*	MIC values of 0.125 and 0.5 μg/mL,	
			Positive control, chloromycetin		MIC value of 0.5 μg/mL.	
			Penicibrocazines H, I (**38-39**),	*V. harveyi*	MIC values of 16.0 and 32.0 μg/mL	
			Positive control chloromycetin		MIC value of 4 μg/mL	
			Penicibrocazines H (**38**),	*E. coli, A. hydrophilia* and *V. parahaemolyticus*	MIC, 16.0, 32.0, and 16.0 μg/ mL	
			Positive control, chloromycetin		MIC, 2.0, 4.0, 2.0 μg /mL	
			Brocapyrrozins A and B (**40-41**), 4-Hydroxy-3-phenyl-1H-pyrrol2(5H)-one (**44**)	*F. xysporum*	MIC, 0.25 64.0 and 0.125 μg/ mL,	
			Positive control zeocin		MIC, 0.5 μg/mL	
20.	*Penicillium brocae* MA-231,	Hainan Island, China	Spirobrocazines A (**48**)	*Escherichia coli, S. aureus* and *Vibrio harveyi,*	MIC, 32.0, 16.0, and 64.0 μg/mL,	Meng *et al*., 2016
			Positive control chloromycetin		MIC, 2.0, 0.5, and 2.0 μg/mL	
			Spirobrocazine B (**49**)			
			Spirobrocazine C (**50**)	A2780 cells	$IC_{50,}$ 59 μM	
			Spirobrocazine C (**50**)	*E. coli, Aeromonas hydrophilia*, and *V. harveyi,*	MIC, 32.0 μg/mL.	
			Brocazine G (**51**)	A2780 and A2780 CisR	$IC_{50,}$ 664 and 661 nM	
			Positive control cisplatin		$IC_{50,}$ 1.67 and 12.63 μM	
			Brocazine G (**51**)	*Staphylococcus aureus*	MIC, 0.25 μg/mL	
			Positive control, chloromycetin		MIC, 0.5 μg/mL	
21.	*Penicillium* sp.FJ-1		(*Z*)-7,4'-dimethoxy-6-hydroxy-aurone-4-O-β- glucopyranoside (**52**),	*Candida* sp., inhibit extracellular phospholipase secretion		Song *et a*l., 2015
22.	*Penicillium citrinum*		(*Z*)-7,4′-dimethoxy-6-hydroxy-aurone-4-O-β-glucopyranoside (**52**)			Liu *et al*., 2015a
			(-)-4-O-(4-O-β-D-glucopyranosylcaffeoyl)quinic acid (**53**),	Chemoreversal activity	Inhibiting P-glycoprotein efflux pump function	
23.	Penicillium sp.FJ-1	Fujian, China	4-(2',3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**54**),	Tca8113 and MG-63 cells	$IC_{50,}$ 26 and 35 μM,	Zheng *et al*., 2014
			15-Hydroxy-6α,12-epoxy-7β,10αH,11βH-spiroax-4-ene-12-one (**55**)	Tca8113, MG-63 and the normal liver cell line WRL-68	$IC_{50,}$ 10, 55 and 58 μM	
			Taxol, the positive control	Tca8113 and MG-63 cell lines	$IC_{50,}$ 46 and 10 nM	
24.	*Penicillium brocae* MA-192	Hainan Island, China	(10R, 14R)-10-Hydroxydihydroresorcylide (**56**), brocaketone A (**57**), brocaketone D (**58**)	DPPH assay	$IC_{50,}$ 14.4, 5.9, and 16.3 μg/ml	Zhang *et al*., 2015
			Positive control BHT		$IC_{50,}$ 18.5 μg /ml	
25.	*Aspergillus versicolor*	Port Safaga, Red Sea Governorate, Egypt	Allantopyrone E (**59**)	HeLa cells	$IC_{50,}$ 50.97 μM	Elsbaey *et al*.2020

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Sr. No.	Fungal strain	Site of Collection	Compounds Isolated	Biological target	Biological active value (IC_{50} /ED_{50})	Reference
26.	*Aspergillus niger* MA-132		Nigerapyrones A-C (**60-62**), Nigerapyrones F-H (**65-67**), Asnipyrones B (**68**)			Liu *et al*,. 2011
			Nigerapyrone B (**61**),	HepG2 cell line	$IC_{50,}$ 62 µM	
			Nigerapyrone D (**63**)	MCF-7, HepG2, and A549 cell lines	$IC_{50,}$ 121, 81, and 81 µM	
			Nigerapyrone E (**64**)	SW1990, MDA-MB-231, A549 MCF-7, HepG2, Du145, NCI-H460, and MDA-MB-231 cell lines	$IC_{50,}$ 38, 48, 43, 105, 86, 86, 43, and 48 µM,	
			Positive control, fluorouracil	A549, HepG2, DU145,MCF-7, SW1990, NCI-H460, and MDA-MB-231 cell lines	$IC_{50,}$ 52, 109, 3.3, 31, 121, 8.5, and 59 µM	
			Asnipyrone A (**69**)	A549 cell line	$IC_{50,}$ 62 µM	
27.	*Aspergillus niger* MA-132		Nigerasterols A(**70**), B (**71**), Malformins A_1 (**72**), C (**73**)	HL60 and A549 cell lines		Liu *et al*., 2013
28.	***Aspergillus versicolor***	17 K Safaga, Red Sea, Egypt	Anthcolorin G **(74),** (7R,8R)-8-hydroxysydowic acid **(76)**, (7S,10S)-10-hydroxy-sydowic acid **(77)**, (7S,11R)-12-hydroxy-sydowic acid **(78)**, (7S,11R)-12-Acetoxy-sydowic acid **(79)**, (7R,8R)-1,8-epoxy-11-hydroxy-sydonic acid **(80)**, 7-deoxy-7,14 –didehydro -11-hydroxysydonic acid **(81)**, (7R)-11-hydroxy-sydonic acid methyl ester **(84)**, 3-hydroxy-4-(1-oxo-ethane) benzoic acid **(85)**, (S)- sydowic acid **(86)**, (7R,10R)-iso-10-hydroxy-sydowic acid **(87)**, Engyodontiumone J **(88)**, engyodontiumone I **(89),** (E)-7-deoxy-7,8-didehydro12-hydroxy-sydonic acid **(90)**, (7R)-11-hydroxysydonic acid **(91)**, an epimeric mixture of (7R,11R), (7R,11S)-12-acetoxy sydonic acid, **(92)**, 12-acetoxy-1-deoxy-sydonic **(93),** Macrosporin **(95)**, Ergostrol peroxide **(96)**			Elsbaey *et al*., 2019
			Anthcolorin H (**75**), 7-deoxy-7,14-didehydro-12-acetoxy-sydonic acid (**82**), (E)-7-deoxy-7,8-didehydro-12- acetoxy-sydonic acid (**83**), Diorcinol (**94**)	Hela cells	$IC_{50,}$ 43.7, 83.8, 53.5, 83.8 µM	
29.	*Stemphylium globuliferum*		Altersolanol Q (**97**), 10-methylaltersolanol Q (**98**), Alterporriol X (**99**), Dihydroaltersolanol B (**100**) and C (**101**), Altersolanol A (**102**), B (**103**), N (**104**), 1-hydroxy3-methoxy-6-methylanthraquinone (**105**), Macrosporin (**95**), Altechromone A (**106**), Alterporriol D (**107**), E (**108**), R (**109**), V (**110**), and W (**111**)			Moussa *et al*,. 2016
			Dihydroaltersolanol C (**101**), Altersolanol A, (**102**) B, (**103**), Alterporriol E (**108**),	L5178Y mouse lymphoma cell line	$IC_{50,}$ 3.4, 2.53, 3.78, and 6.9, µm	Debbab *et al*. ,2009; Liu *et al*., 2015b
			Altersolanol N (**104**)	L5178Y cells	IC_{50} values in the low micro-molar range	Debbab *et al*., 2012
			altersolanol A (**102**)	34 human cancer cell lines	Mean IC_{50} (IC_{70}) values of 0.005 µg/mL(0.024 µg/mL).	Mishra *et al*., 2015
30.	*Cladosporium oxysporum*	Hainan Province, China	Thiocladospolides F-J (**112-116**), Pandangolide 3 (**117**), Thiocladospolide A (**118**), Seco-secopatulolide C (**119**), and Iso-cladospolide B (**120**)	*Edwardsiella tarda* and *E. ictarda*	MIC values ranging from 4 to 32 µg/mL.	Wang *et al*., 2020
			Thiocladospolide G (**113**)	*E. tarda*	MIC, 4 µg/mL	
			Iso-cladospolide B 120 (**120**)	*Cytospora mandshurica*	MIC, 8 µg/mL	
31	*Phoma* sp. SK3RW1M	Shankou mangrove, Guangxi, P. R. China	1,8-dihydroxy-10-methoxy-3-methyldibenzo[b,e]oxepine-6,11-dione 121 (**121**), 1-hydroxy-8-(hydroxymethyl)-6-methoxy -3-methyl -9H- xanthen-9-one 122 (**122**), 1-hydroxy-8-(hydroxymethyl)-3-methoxy-6-methyl-9H-xanthen -9-one 123 (**123**),	Cytotoxic	Inactive	Pan *et al*., 2010
32	*Xylaria* sp. (No. 2524)		Cyclo-(L-Phe-L-Leu1-L-Leu2-L-Leu3-L-Ile) (**124**), (3S,4R)-dihydroxy-(6S)-undecyl-α-pyranone (**125**)	Bel-7402, NCI-4460 and L-02 cell lines	Poorly active	Li *et al*., 2004
33.	Endophyte No. 2106	Hong Kong	2106 A (**126**), Cyclo-(N-MeVal-N-MeAla) (**127**)	-	-	Wang *et al*., 2008
34.	Unidentified endophytic fungus	Oman	Farinomalein (**128**), Farinomaleins B-E (**129-132**), (3R)-5,7-dihydroxy-3-methylisoindolin-1-one. (**133**)			El Amrani *et al*., 2012
			Farinomaleins B (**129**)		$IC_{50,}$ 4.4 µg/mL	
35.	Endophytic fungus (No. ZH19)	Dong Sai of the South China Sea coast	1,7-Dihydroxy-2-methoxy-3-(3-methylbut-2-enyl) -9H–xanthen -9-one (**134**)	KB and KBV200 cells	$IC_{50,}$ 20 and , 30 µM	Huang *et al*,. 2010
			1-Hydroxy-4,7-dimethoxy-6-(3-oxobutyl) -9H-xanthen9-one (**135**).	KB and KBV200 cells	$IC_{50,}$ 35 and 41 µM	

and *Colletotrichum gloeosprioides* 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, penicibrocazines A-E (**23-27**) (**Fig. 3**), along with previously isolated congener phomazine B (**28**) (**Fig. 4**), were purified from *Penicillium brocae* 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 *Gaeumannomyces 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 IC_{50} 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, penicibrocazines 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-hydroxy-phenopyrrozin (**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 *V. 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 IC_{50} values of 6.64 and 6.61 µM, respectively, which was found better than cisplatin (positive control) with $IC_{50,}$ value of 1.67 and 12.63 µM, respectively. In addition,

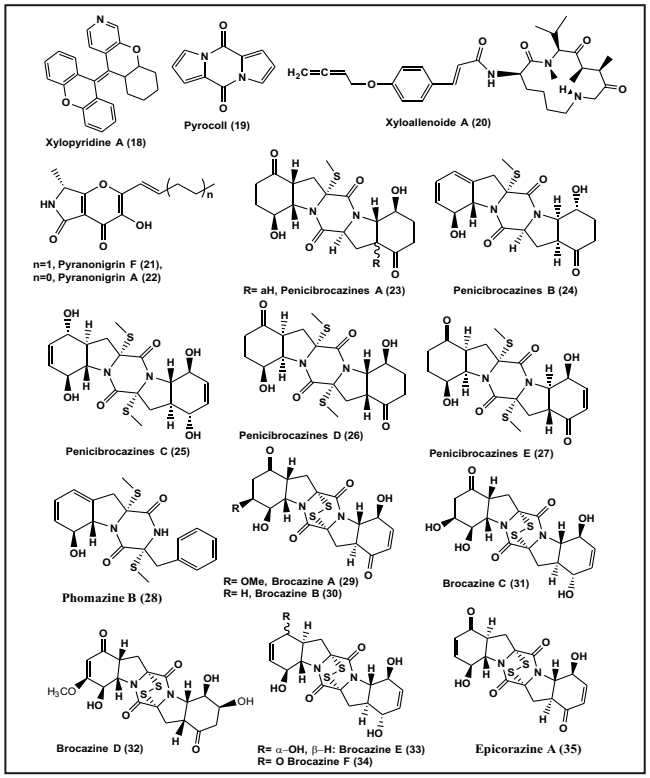

Fig. 3. Bio-actives reported from *Xylaria* sp. (18-20) and *Penicillium* sp. (21-35) an endophyte from *A. marina*.

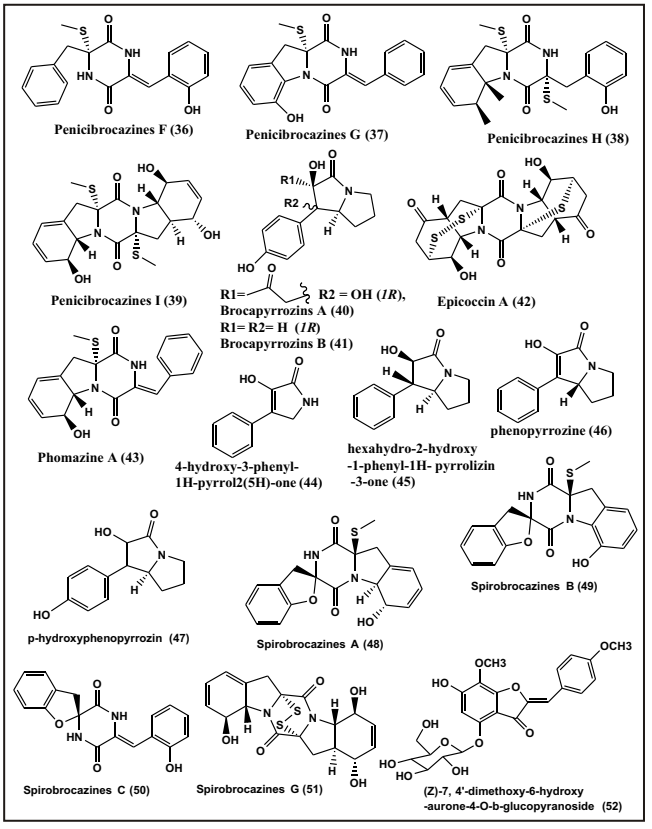

Fig. 4. Bio-actives reported from *Penicillium* sp. (36-52) an endophyte from *A. marina*

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-ß-glucopyranoside (**52**) (**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-ß-glucopyranoside (DHAG) (**52**) and (-)-4-O-(4-O-ß-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 H_2O_2-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). DHAG (**52**) exerted anti-inflammatory effects by inhibiting inflammatory factors including the pro-inflammatory mediator NO and the pro-inflammatory cytokines IL-1b and TNF-a in LTA-stimulated H9c2 cells. Moreover, DHAG (**52**) considerably suppressed pro-inflammatory molecule production from upstream signaling pathways, which were involved in the progression of inflammatory responses in H9c2 cells. Activation of NF-jB and MAPK leads to transcription factor binding to the promoter regions of pro-inflammatory cytokine genes, thereby enabling transduction of extracellular signals into cellular reactions (Dong *et al.*, 2002). DHAG (**52**) decreased phosphorylation of several MAPKs, including JNK and P38, whose phosphorylation was induced by LTA stimulation. In addition, DHAG reduced nuclear translocation of NF-jB in response to LTA. It is also demonstrated that DHAG, LTA induced oxidative stress and inflammatory responses in cardiomyoblasts (Song *et al*., 2020).

Two new compounds, named as 4-(2',3'-dihydroxy-3'-methyl-butanoxy)-phenethanol (**54**), and 15-hydroxy-6a,12-epoxy-7ß,10aH,11ßH-spiroax-4-ene-12-one (**55**) (**Fig. 5**), were isolated from the endophytic fungus *Penicillium* sp.FJ-1 of mangrove *A. marina* collected in

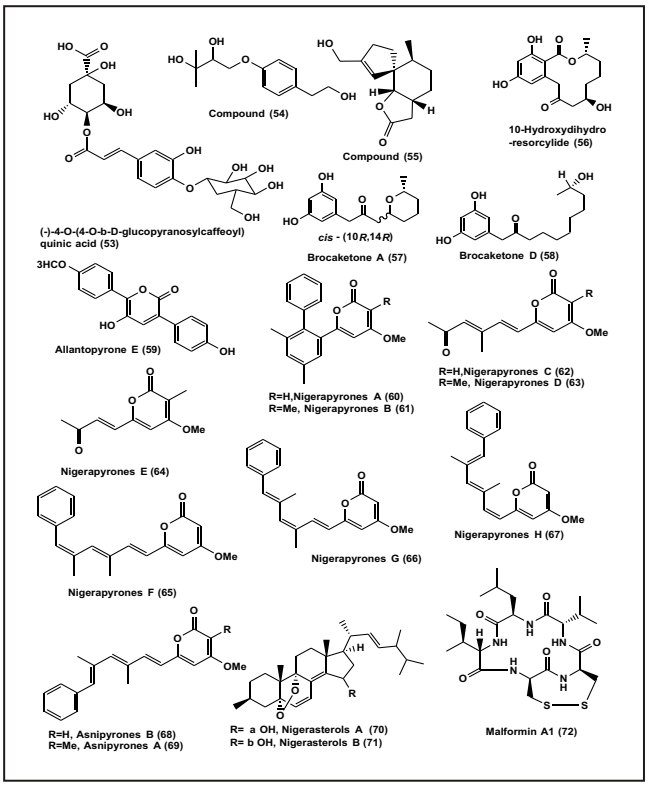

Fig. 5. Bio-actives reported from *Penicillium* sp. (53-58) and *Aspergillus* sp. (59-72) endophyte from *A. marina*

Fujian, China. Compound (**55**), displayed activity against Tca8113, MG-63 and WRL-68 cells with an IC_{50} 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 week activity with IC_{50} values of 26 and 35 µM, against Tca8113 and MG-63 cells, respectively. Positive control taxol, displayed cytototoxicity against Tca8113 and MG-63 cell lines with IC_{50} 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. brocae* 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 IC_{50} values of 14.4, 5.9, and 16.3 µg/mL, respectively, while positive control BHT displayed scavenging activity with IC_{50} 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 IC_{50} value of 50.97 µM (Elsbaey *et al*., 2020).

Eight new a-pyrone derivatives, nigerapyrones A-B (**60, 61**), (**Fig. 5**), C-E (**62-64**) and nigerapyrones F-H (**65-67**), together with previously reported congeners, asnipyrones B (**68**) and A (**69**) (**Fig. 6**), were purified from endophytic fungus *A. niger* MA-132, residing inside the fresh tissue of mangrove plant *A. 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, 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 nigerapyrone 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 *A. niger* MA-132, residing inside the mangrove plant *A. 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.

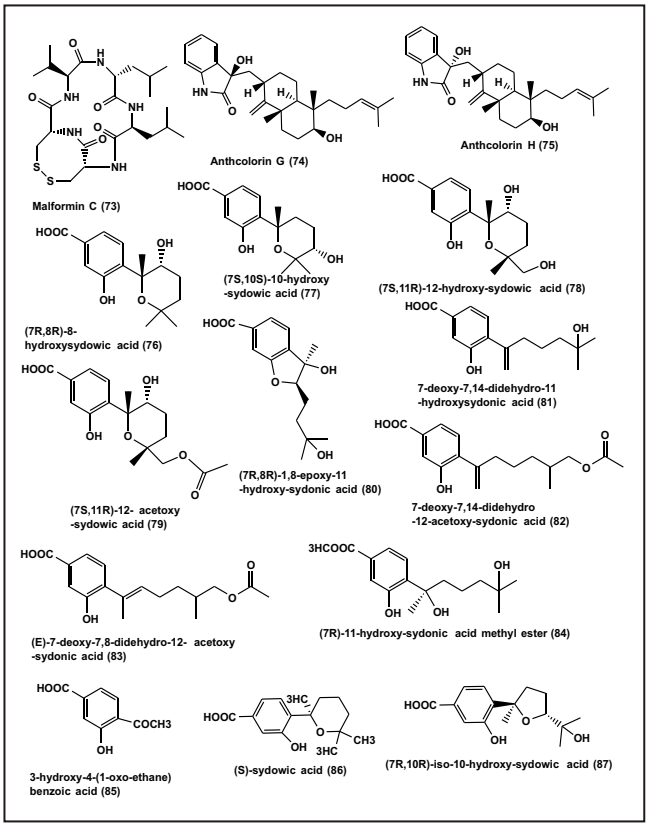

Fig. 6. Bio-actives reported from *Aspergillus* sp. (73-87) endophyte from *A. marina*

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 oxoindolo 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,11R)-12- acetoxy-sydowic acid (**79**), (7R,8R)-1,8-epoxy-11-hydroxy-sydonic acid (**80**), 7-deoxy-7,14–didehydro -11-hydroxysydonic 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 (S)-sydowic acid (**86**), (7R,10R)-iso-10-hydroxy-sydowic acid (**87**), engyodontiumone J (**88**), engyodontiumone I (**89**), (E)-7-deoxy-7,8-didehydro12-hydroxy-sydonic acid (**90**), (7R)-11-hydroxysydonic acid (**91**), an epimeric mixture of (7R,11R) and (7R,11S)-12-acetoxy sydonic acid (**92**), 12-acetoxy-1-deoxy-sydonic (**93**), diorcinol (**94**), macrosporin (**95**), and ergostrol peroxide (**96**) (**Fig. 7**), were purified from endophytic fungus *Aspergillus versicolor* isolated from mangrove plant *A. marina* and grown on the solid rice culture. The site of collection was 17 K Safaga, Red Sea, Egypt.

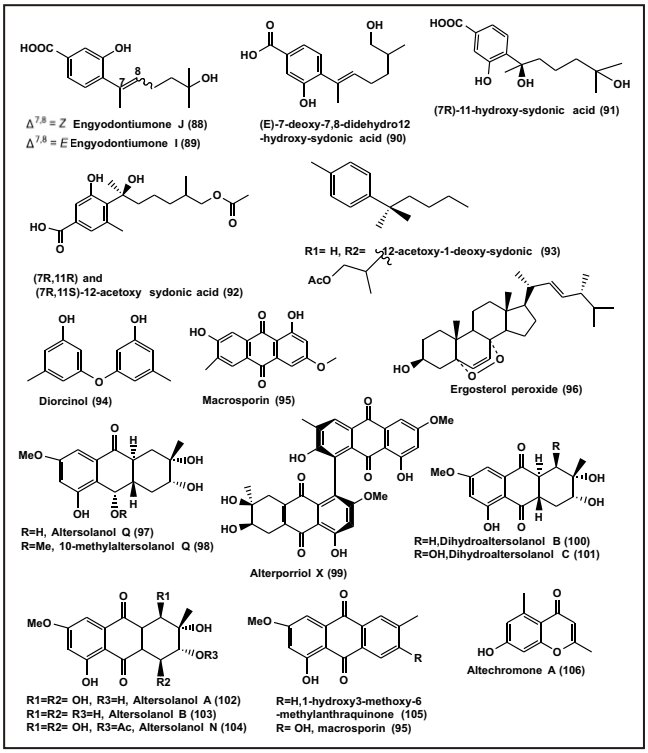

Fig. 7. Bio-actives reported from *Aspergillus* sp. (87-96) sand *Stemphylium* sp. (97-106) endophyte from *A. marina*

Compounds (**75, 82, 83** and **94**), were found active with IC_{50} values of 43.7, 83.8, 53.5, 83.8 µM, respectively against Hela cell lines (Elsbaey *et al*., 2019).

COMPOUNDS 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-hydroxy3-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_{50} values of 3.4, 2.53, 3.78, and 6.9, µM, respectively (Debbab *et al*., 2009; Liu *et al*., 2015b). Compound (**104**) also exhibited potent cytotoxicity against L5178Y cells with IC_{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_{50} values of 0.005 µg/mL (Mishra *et al*., 2015).

Five novel 12-membered macrolides containing thioethers, thiocladospolides F-J (**112-116**), along with previously isolated analogues, pandangolide 3 (**117**), thiocladospolide A (**118**), seco-secopatulolide C (**119**), and iso-cladospolide 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 µg/mL against *Edwardsiella tarda* and *E. ictarda*, the aquatic pathogens. Compound (**113**) exhibited potent activity against *E. tarda* with MIC values of 4 µg/mL and compound (**120**) was found active against plant pathogenic fungus *Cytospora mandshurica* with MIC values of 8 µg/mL (Wang *et al*., 2020).

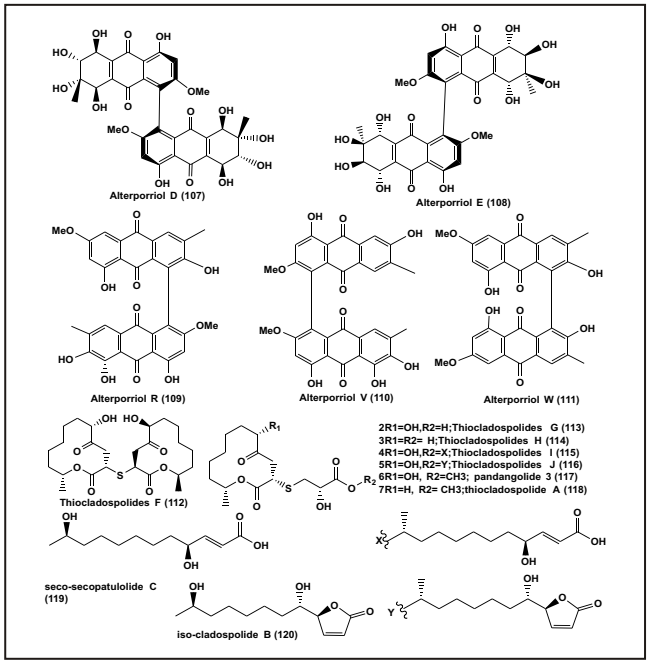

Fig. 8. Bio-actives reported from *Stemphylium* sp. (107 - 111) and *Cladosporium* sp. (112-120) endophyte from *A. marina*

A new lactone, 1,8-dihydroxy-10-methoxy-3-methyldibenzo [b,e]oxepine-6,11-dione (**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)-undecyl-a-pyranone (**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 L-02 the normal human cell lines (Li et al., 2004). 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

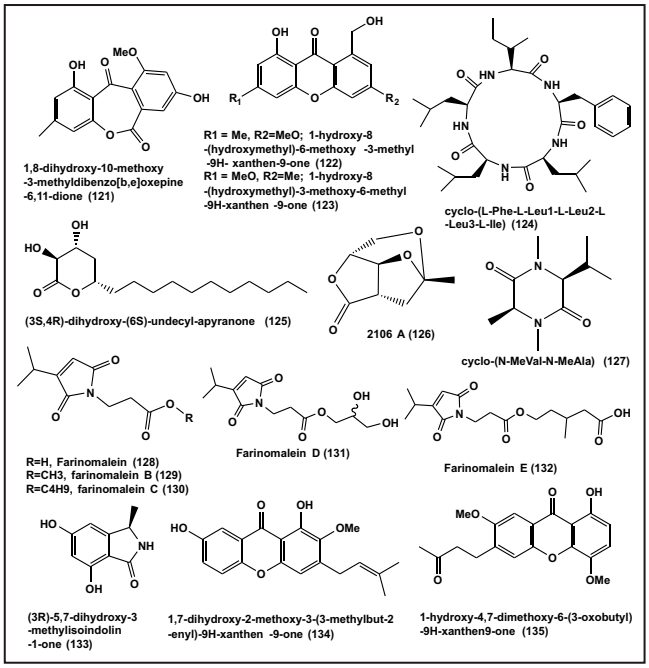

Fig. 9. Bio-actives reported from *Phoma* sp. (121 -123) and Unidentified endophytes (124-135) from *A. marina*

with three new farinomalein derivatives, farinomaleins B-E (**129-132**), and one new isoindoline congener (3R)-5,7-dihydroxy-3-methylisoindolin-1-one. (**133**) (**Fig. 9**), were extracted from an unidentified endophytic fungus residing inside the inner tissues of plant *A. marina* from Oman. Only compound (**129**) displayed average cytotoxicity against L5178Y cells with IC_{50} value of 4.4 µg/mL (El Amrani *et al*., 2012).

Two new xanthone derivatives, 1,7-dihydroxy-2-methoxy-3-(3-methylbut-2-enyl)-9H -xanthen-9-one (**134**) and 1-hydroxy-4,7-dimethoxy-6-(3-oxobutyl) -9H-xanthen9-one (**135**) (**Fig. 9**), were purified from the mangrove endophytic fungus (No. ZH19) residing inside the leaves of *A. marina* from the Dong Sai of the South China Sea coast. Compounds (**134**) displayed cytotoxicity against KB and KBV200 cells with IC_{50} values of 20 and 30 µM while compound (**135**) was found active against both the cells with IC_{50} values of 35 and 41 µM, respectively (Huang *et al*., 2010).

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, macrolide, etc. (**Table 2**). Some of the isolated compounds, viz. (Z)-7,4'-dimethoxy-6-hydroxy–aurone-4-O-ß-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 (NSG) 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.

Table 2. Chemical class of various metabolites identified from Endophytic fungi of *Avicennia marina*

Species	Class	Metabolite	Reference
Xylaria sp. (no. 2508)	Phenolic	10	Lin *et al*., 2001a
Xylaria sp. (no. 2508)	Allenic ethers	11-13	Lin *et al*., 2001b
Xylaria sp. (no. 2508)	Benzofuran	17	Xu *et al*., 2008
Xylaria sp. (2508)	Pyridine	18	Xu *et al*., 2009
Penicillium brocae MA-231	Pyran	21,22	Meng *et al*., 2015a
P. Brocae ma-231	Piperazine	23-27	Meng *et al*., 2015b
P. Brocae ma-231	Piperazine	29-34	Meng *et al*., 2014
P. Brocae ma-231	Piperazine	36-39	Meng *et al*., 2017
P. Brocae ma-231	Pyrrozin	40,41	Meng *et al*., 2017
P. Brocae ma-231	Pyrrol	44	Meng *et al*., 2017
P. Brocae ma-231	Piperazines	48-51	Meng *et al*., 2016
Penicillium sp.FJ-1	Glycoside	52	Song *et al*., 2015
Penicillium citrinum	Glycoside	53	Song *et al*., 2020
Aspergillus versicolor	Pyrone	59	Elsbaey*et al*.,2020
Aspergillus niger MA-132	Pyrone	60-69	Liu *et al*., 2011
A. Niger ma-132	Sterol	70, 71	Liu *et al*., 2013
A. Niger ma-132	Cyclopeptides	72, 73	Liu *et al*., 2013
Aspergillus versicolor	Terpene	74-83	Elsbaey *et al*., 2019
Aspergillus versicolor	Benzoic acid	85	Elsbaey *et al*., 2019
Aspergillus versicolor	Sydowic acid	86, 87	Elsbaey *et al*., 2019
Aspergillus versicolor	Sydonic acid	90-93	Elsbaey *et al*., 2019
Aspergillus versicolor	Ergostrol	96	Elsbaey *et al*., 2019
Stemphylium globuliferum	Solanol	97, 98, 100-104	Moussa *et al*., 2016
Stemphylium globuliferum	Anthraquinone	105	Moussa *et al*., 2016
Cladosporium oxysporum	Macrolide	112-116	Wang *et al*., 2020
Phoma sp. SK3RW1M	Lactone	121	Pan *et al*., 2010

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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