- Review paper

Cytotoxic Compounds Derived from Marine Algicolous and Spongicolous Endophytic Fungi: A Review

Nadia Tasnim Ahmed[1], Sadia Noor[1], Md Mustafizur Rahman[2] and Md. Abdul Mazid[1]

[1]Department of Pharmaceutical Chemistry, University of Dhaka, Dhaka-1000, Bangladesh
[2]Pharmacy Discipline, Khulna University, Khulna-9208, Bangladesh

(Received: August 26, 2021; Accepted: December 20, 2021; Published (web): December 26, 2021)

ABSTRACT: Endophytes have gained particular interest in the search of potential pharmaceutical candidates for a long time due to their diversity, species richness and bioprospecting nature. They generally produce the essential metabolites for their expansion inside the plant which is involved in various biotransformation processes of utilizing host nutrients and cell components to continue microbial growth, sustenance, and reproduction. In above processes, they produce a huge amount of both structurally and functionally diverse secondary metabolites for maintaining an effective symbiosis with hosts. These compounds are proven to have significant bioactive properties like antibacterial, antifungal, antiviral, anti-inflammatory, antioxidants, antitumor activities. Despite the proven significance, a little is exploited so far about endophytes. Particularly marine fungal endophytes which are the centre of attention in this review have gained much less importance. Due to unique environmental feature, fungal endophytes derived from marine environment offer vast diversity in different bioactive secondary metabolites. This review has focused on algicolous endophytes and bioactive secondary metabolites discovered during the last two decades. Particular importance has been given to cytotoxic and antimicrobial metabolites. Due to intensive studies during last several years, an extensive number of publications are now available on cytotoxic compounds derived from endophytic fungi of marine algicolous and spongicolous origin that have been summarized in this review.

Key words: Endophytic fungi, Cytotoxic compounds, Bioactive secondary metabolites, Marine algicolous and spongicolous endophytes

Endophytes and Endophytism

Endophytes are either bacterial (including actinomycetes) or fungal microorganism. These endophytes spend the whole or part of their life cycle living inter- and/or intra-cellularly inside the healthy tissues of the host plant.[1] They are non-organ specific, can invade any plant organs and reside beneath the epidermal cells of plants.[2-4] There is no apparent evidence of their existence in plants because they neither cause any noticeable tissue damage nor produce any symptoms.[5] They may be present ubiquitously in each and every healthy plant usually more than one in each flora through a symbiotic association with the host.[6,10] In general, bacteria, archaebacteria, fungi, algae, mycoplasma all can act as endophytes. They are prolific sources of bioactive metabolites which they produce via direct association with their hosts.[10] Our main focus for this review is fungi or mycoendophytes derived from or associated with marine sources i.e., macroalgae, and bioactive secondary metabolites obtained from them.

Correspondence to: Md. Abdul Mazid
Email: ma.mazid@du.ac.bd

Dhaka Univ. J. Pharm. Sci. **20**(2): 247-265, 2021 (December)
DOI: https://doi.org/10.3329/dujps.v20i2.57175

Algicolous Fungi

Marine algae usually contribute one-third of well known higher fungal endophytes. For more than 2000 years, macroalgae have been widely exploited traditionally in China and ancient Egypt as folk medicine. Most algicolous marine fungi are Ascomycetes. For adaption with the constant environmental stress of marine atmosphere such as frequent change in moisture and salt concentration, sunlight exposure for prolonged time, tide alteration, abundant microorganisms and herbivore insects, etc.,

it apparently looks like that both marine algae and their endophytic symbionts could be a significant source of secondary metabolites having biological activities.[7]

Isolation and cultivation of fungi from marine organisms

As a general approach, surface sterilizaiton techniques are employed to isolate endophytes from marine algae. Initially, epiphytes inhabited in the outer surface of algae are removed by this sterilization process. The surface sterilization are done in different ways depending on microbial species and/or host tissue types. Several mechanical processes such as ultrasonic bath sonication, ultrasonic probe sonication, use of beads and vortexing; using enzymes such as proteinase K, lysozyme; and chemicals such as bleaching agent, ethanol, alkaline lysis buffer, UNSET buffer, CTAB buffer, bactericidal cleanser, etc. have been used by scientists to eliminate epiphytes completely from the sample surface as per suitability.[8] Researcher usually choose healthy and disease free fresh algae for isolation purpose. This is important to avoid isolation of localized pathogens and saprophytic microbes.[9,10] Moreover, to eleminate contamination by air microspores, samples after collection are needed to be processed immediately or stored at 4°C in case of delayed processing.[11,12] The most commonly used approaches followed reserachers for the isolation and cultivation of endophytic fungi are summarized below.[13]

1. Cutting of samples (sponge tissues, mangrove leaves, algal biomass, etc.) into small pieces and removing debris adherent to the surface by rinsing with sterile seawater.
2. Immersing the pieces of sample in 70% ethanol for surface sterilization. This is to be done carefully to avoid any tissue damage of the sample. To check sterilization effectiveness, it is recommended to take imprints of the tissues on growth medium. Lack of microbial growth will indicate successful sterilization.
3. After drying with a sterile cotton cloth, pieces are streaked over a petri dish containing culture media (such as water agar medium), then again cut into smaller pieces.
4. These pieces are then incubated in media (water agar medium) amended with antibiotics at 20-25°C under daylight.
5. After two weeks of incubation, different fungal strains are developed from sample. Hyphal tips of growing fungi are transferred in second media such as potato dextrose agar medium (PDA) for further growth.
6. Isolated pure strains are taxonomiclly identified by observing morphological characteristics, and by DNA amplification and sequencing of the fungal internal transcribed spacer (ITS) region.

Extraction and characterization of endophytic fungal metabolites

Various fermentation techniques such as shaking or static culture of endophytes at optimized conditions including temperature, light, aeration, etc. are maintained for compound extraction.[14,15] Fermentation media viz. PDA medium, malt extract medium, liquid Wickerham's medium, etc. are mostly utilized for effective large scale production of bioactive compound.[13] Separation of mycelia and filtrate is done by filtration followed by extraction of the compound using appropriate organic solvents. Most widely used solvent for this purpose is ethyl acetate. Other solvents used are methanol, dichloromethane, chloroform and hexane, etc.[16,19]

Cell-free organic phase is dried under vacuum at 40°C by a rotary evaporator. Fractionation of extracts is done using column chromatography by polarity based gradient elution of the suitable solvent system, and the existence of the compounds is detected by thin layer chromatography (TLC). Further isolation proceeds by preparative TLC, column chromatography, vacuum liquid chromatography or preparative-HPLC, etc. Elucidation of compound structure is carried out using high-resolution nuclear magnetic resonance (NMR) and fourier transform ion cyclotron resonance mass spectrometry (FT-ICR/MS)

etc. Liquid chromatography-mass spectrometry (LC-MS) is also used for compound identification by correlating both molecular weight and UV absorption data. When the individual compounds are purified and structurally recognized, they are then assayed for bioactivity such as cytotoxicity, antimicrobial activity, etc.

Biological potentials of endophytic fungal metabolites

Metabolic interactions between endophytes and hosts like signaling defense and regulation of symbiosis for adaptation in the highly competitive environment lead to the production of varieties compounds but very little is known about exact biosynthetic pathways behind those. Until now, several hundreds of bioactive metabolites have been identified and isolated from endophytic fungi having a wide range of properties including anticancer, antimicrobial, immunosuppressants activities, etc. (Table 1). World's first billion-dollar anticancer drug taxol shifted natural product research to endophytic fungi initially which could be derived only from some slow-growing rare yew trees. An endophytic fungus, *Taxomyces andreanae* isolated from yew tree, *Taxus brevifolia* Nutt. had been reported of having the capability to produce taxol for the first time in 1971 by Wani *et al.*[11] In search of other taxol producing endophytes from different other species of yew tree, an endophytic fungus *Pestalotiopsis microspora* isolated from *Taxus wallachiana* by Strobel *et al*. has drawn attention.[20] Cephalosporin C, another very significant discovery of the era was isolated from marine-derived fungus *Acremonium chrysogenum*. Till now, more than 1000 novel natural compounds have been discovered by exploring marine-derived fungi haveing new carbon skeleton which indicates marine-associted fungi as a promising source of pharmaceutical lead compounds. Among different genus, *Aspergillus* and *Penicillium* are two prolific producers of new metabolites.

Cytotoxic metabolites from marine algicolous endophytic fungi

Polyketides

Few dozens of polyketides having cytotoxicity have been isolated from marine algicolous endophytic fungi. A berif of the important endophytes, their sources and isolated cytotoxic metaboliotes are summarized in Table 1. Elsebai *et al*. found seven novel phenalenone derivatives (**1-7**) from the endophyte *Coniothyrium cereal* derived from *Enteromorpha* sp., a green alga obtained from Fehmarn of Baltic Sea. Among the separated compounds, coniosclerodorolide (**1**) has been showed powerful inhibition of human leukocyte elastase (HLE) having the IC_{50} value of 13.3 µM.[36] Marine alga *Ceramium* sp. derived endophytic fungus *Phaeosphaeria spartinae* was investigated which provide the isolation of a novel compound spartinoxide (**9**) and two known compounds 4-hydroxy-3-prenyl-benzoic acid (**10**) and anofinic acid (**8**). Compounds **9** and **10** have been proved to be the potent inhibitor of HLE having IC_{50} values of 1.71 ± 0.30 µg/ml (6.5 µM) and 1.67±0.32 µg/ml (8.1 µM), respectively.[37] The red alga *Carpopeltis cornea* (collected in Ulsan City, Korea) derived endophytic fungus *Aspergillus parasiticus* # MFA 153 was cultivated which led to the isolation of a novel gabosine derivative parasitenone (**11**), having moderate antioxidative activity.[38] Anomalins A (**12**) and B (**13**), two xanthone derivatives were isolated from a culture of the endophyte *Wardomyces anomalus* OS4T3-2-1 from the green alga *Enteromorpha* sp. (collected around Fehmarn island in the Baltic Sea). Anomalin A (**12**) found active significantly as a p56(lck) tyrosine kinase inhibitor and also as an antioxidant.[3] *Aspergillus pseudodeflectus* Hiji005 derived from brown alga *Sargassum fusiform* (collected in the Miura Peninsula, Japan) produced a new cytotoxic isochroman metabolite, pseudodeflectusin (**14**). This isolated metabolite showed moderate but selective cytotoxicity against several human cancer cell lines including the stomach (NUGC-3), cervix (HeLa-S3),

Table 1. Major classes of bioactive compounds derived from marine associated endophytic fungi.

	Host	Endophyte	Scientist	Compounds	Target action	Ref.
1.1 Anticancer Agents	*Torreya taxifolia*	*Pestalotiopsis microspore*	Lee *et al*., 1996	Torreyanic acid	Sensitive to protein kinase C agonists and causes cell death by apoptosis	21
	Medicago sativa and *Medicago lupulina*	*Phoma medicaginis*	Weber *et al*., 2004	Brefeldine A	Apoptosis in cancer cells	22
	--	*Trametes hirsute*	Puri *et al*., 2006	Podophyllotoxins	Exhibit potent antioxidant, anticancer, and radioprotective properties	117
1.2 Antimicrobial Agents	--	*Cryptosporiopsis cf. quercina*	Strobel *et al*., 1999b	Cryptocandin	Against *Candida albicans* and *Trichophyton* sp.	24
	--	*Pestalotiopsis microspore*	Li *et al*., 2001	Ambuic acid Pestaloside Pestalotiopsins A and B	Antifungal	25
	--	*Pestalotiopsis jesteri*	Li and Strobel, 2001	Jesterone	Antifungal activity	26
	--	*Pestalotiopsis adusta*	Li *et al*., 2008a	Pestalachlorides A	Against three plant pathogenic fungi, *Fusarium culmorum*, *Gibberella zeae*, and *Verticillium alboatrum*	27
1.3 Antioxidant Agents	*Terminalia morobensis*	*P. microspore*	Strobel *et al*., 2002	Pestacin Isopestacin	Potent antioxidant activity	34
	Trachelospermum jasminoides	*Cephalosporium* sp. *IFB-E001*	Song *et al*., 2005	Graphislactone A	Antioxidant and free radical-scavenging activity	118, 28
	Pilgerodendron uviferum	*Microsphaeropsis olivacea*	Hormazabal *et al*., 2005			
1.4 Antiviral Agents	--	*Cytonaema* sp.	Guo *et al*., 2000	Cytonic acids A and B	Novel human cytomegalovirus (hcmv) protease inhibitors	29
	--	*Xylaria mellisii*	Pittayakhajonwut *et al*., 2005	Mellisol 1,8-dihydroxy-naphthol 1-O-a-glucopyranoside	Against herpes simplex virustype 1	30
	Quercus coccifera	Associated with leaves	Singh *et al*., 2004	Hinnuliquinone	Potent inhibitor of human immunodeficiency virus type 1 (HIV-1) protease	31
1.5 Antidiabetic Agents	--	*Pseudomassaria* sp.	Zhang *et al*., 1999	Nonpeptidal L-783, 281	Found to act as insulin, with advance that it is not destroyed in the digestive tract and may be given orally	32
	--	*Pseudomassaria* sp.	Salituro *et al*., 2001	Demethyl asterriquinone B-1	Insulin-mimetic compound	33
1.6 Immunossive Agents	--	*Fusarium subglutinans*	Lee *et al*., 1995	Subglutinol A and B	As potent as the immunosuppressant drug cyclosporin A	119
	--	*Colletotrichum dematium*	Ren *et al*., 2008	Collutelin A	Inhibited CD4 (+) Tcell activation of Interleukin 2 production	35

"--" = host not mentioned; Ref. = Reference No.

and peripheral blood (HL-60), with LD_{50} values of 49, 47, and 39 µM, respectively.[40] A *Cladosporium* species L037 derived from the brown alga *Actinotrichia fragilis* (collected from Seragaki Beach at Okinawa Island, Japan) yielded two 12-membered macrolides, sporiolides A (**15**) and B (**16**), that showed powerful cytotoxic activity against murine lymphoma L1210 cells.[41] A known fungal metabolite, 4-Ketoclonostachydiol (**17**) having potent cytotoxic activity, was obtained from an endophyte *Gliocladium* sp. isolated from the New Zealand alga *Durvillaea Antarctica*.[42] A culture of an endophyte *Chaetomium globosum*, derived from the red alga *Polysiphonia urceolata* (collected from Qingdao coastline, China), provided the isolation of a new benzaldehyde secondary metabolite, chaetopyranin (**18**) which exhibited moderate cytotoxicty against three human tumor cell lines, with IC_{50} values of 48.7 (human microvascular endothelial cells, HMEC), 90.2 (hepatocellular carcinoma cells, SMMC-7721), and 123.7 µM (human lung epithelial cells, A549), along with free radical-scavenging activity.[43] Same species was isolated that produce a novel benzonaphthyridinedione derivative, chaetominedione (**45**) having remarkable activity as p56 (lck) tyrosine kinase (93.6% enzyme inhibition at 200 µg/ml) inhibitor.[44] Cultivation of marine green alga-derived endophyte *Monodictys putredinis* (No. 187/195 15 I, collected from Tenerife, Spain) resulted to the isolation of four monomeric xanthones, including monodictysins A-C (**19-21**) and monodictyxanthone B (**22**) as well as a benzophenone monodictyphenone C (**23**). Among them, monodictysin B (**20**) showed cytochrome P450 1A inhibition, while monodictysin C (**21**) moderately induced NAD(P)H: quinine reductase (QR) activity in mouse Hepa 1c1c7 cells. Also, monodictysin C (**21**) inhibited aromatase activity weakly.[45] After fermentation of a culture of a *Curvularia* sp. (strain no. 768) isolated from the red alga *Acanthaphora spicifera* (collected in Apra Harbor, Guam), a novel macrolide apralactone A (**24**), a 14 membered phenyl acetic acid macrolactone, and the antipodes of curvularin macrolides (**25-27**) were identified. These isolated metabolites showed cytotoxicity against several human tumor cell lines.[46] *Penicillium chrysogenum* QEN-24S, obtained from the red alga *Laurencia* sp. (collected from the Weizhou Island, South China Sea), produced two polyketide penicitides A (**28**) and B (**29**) and the glycerol derivative. Penicitide A displayed moderate cytotoxic activity against the human hepatocellular liver carcinoma cell line with an IC_{50} value of 111.9 µM.[47]An endophyte *Aspergillus terreus*, derived from the red alga *Laurencia ceylanica* (from East coast of Sri Lanka), was a producer of a new butyrolactone (**30**), which exhibited significant inhibition of the β-glucuronidase enzyme having IC_{50} value of 6.2 µM.[48] A culture of an endophyte *Paecilomyces variotii* EN-291 obtained from the red alga *Grateloupia turuturu* (from Qingdao, China) was fermented that led to the isolation of two new butenolides, butyrolactone IX (**31**) and aspulvinone O (**32**). Between these, aspulvinone O was found as a significant antioxidant having IC_{50} value of 11.6 µM.[49] Halimide alkaloids were produced by *Aspergillus* sp. CNC139 isolated from a sample of the green alga *Halimeda copiosa*. Halimide (**33**) was shown to inhibit the growth of colon cancer and ovarian cancer cell lines with IC_{50} values of 1 and 0.8 µM, respectively.[50] The fungus *Emericella nidulans* var. *acristata* was isolated as an endophyte from a Mediterranean green alga. Cultivation of this fungus yielded two new compounds, arugosins G (**34**) and H (**35**), together with the known metabolites arugosins A (**36**) and B (**37**). Arugosins A and B exhibited cytotoxic activity towards seven cell lines at the concentration of 10 µM.[16] Cultivation of endophyte *Monodictys putredinis* derived from a marine alga resulted to the production of two new dimeric chromanones (**38, 39**) consisting two uniquely modified xanthone-derived units. The compounds (**38, 39**) were examined for their cancer chemopreventive potential and shown to inhibit cytochrome P450 1A activity (IC_{50} values of 5.3 and 7.5 µM, respectively). In addition, both compounds displayed moderate activity as inducers of NAD(P)H:quinone reductase (QR) in cultured mouse Hepa 1c1c7 cells.[51] Noduliprevenone (**40**)

isolated from *Nodulisporium* sp. was found to be an inhibitor of P450 (CYP1A), and concomitantly induces NAD(P)H:quinone reductase (QR).[52] An alga-derived endophytic fungus *Penicillium* sp. i-1-1 produced a novel tricyclic compound, citrinal A (**41**) having a rare tetrahydro-2H-benzofuro[7-b][1,4]dioxin-9(3H)-one skeleton. Citrinal A exhibited cytotoxicity against the A-549 and HL-60 cell lines.[53] Cytochalasin D (**42**) , a known antitumor and antibiotic compound was isolated from *Xylaria* sp. strain obtained from Brazilian marine red alga *B. tenella*.[54] Epiepoxydon (**43**) exhibited significant cytotoxicity against human cancer cell lines was obtained from marine fungus *Apiospora montagnei* isolated from the inner tissue of the North Sea alga *Polysiphonia violacea*.[14] An endophyte *Ascochyta saliconiae* obtained from green alga *Ulva* sp. produced 2, 3-dihydro-2-hydroxy-2, 4- dimethyl-5-trans-propenylfura-3-one (**44**) showing inhibitory activity towards tyrosine kinase enzyme.[55] (Table 2, Figure 1)

Terpenoids

Cytotoxic terpenoids reported so far from marine algicolous endophytes are summarized in Table 3 and Figure 2. Four novel derivatives of hydroxylated sclerosporin were isolated from the fungus *Cadophora malorum* (SY3-1-1MIT), collected from the green alga *Enteromorpha* sp. These are 15-hydroxysclerosporin (**45**), 12-hydroxysclerosporin (**46**),11-hydroxysclerosporin (**47**), and 8-hydroxysclerosporin (**48**). Among others 8-Hydroxysclerosporin was found with a weak lipid-accumulation inhibitory activity against 3T3-L1 murine adipocytes.[56] Brown alga *Sargassum horneri* (Wenzhou island, China) derived endophytic fungus *Pestalotiopsis* sp. Z233 was cultured under abiotic stress stimulated by $CuCl_2$. This culture extracts provided two new stress metabolites, eudesmane sesquiterpenes (**49**) and (**50**), which exhibited inhibitory activities against tyrosinase enzyme (IC_{50} values of 14.8 and 22.3 µM respectively).[57] The fungus *Penicillium chrysogenum* QEN-24S was isolated from the marine red alga *Laurencia* sp. Extraction of this fungal culture led to the isolation of two new tetracyclic diterpenes of the rarely reported cyclopiane class, conidiogenones H and I, along with five related congeners, conidiogenones B - D and F and conidiogenol. Among those conidiogenone C (**51**) was found with potent cytotoxic activity against HL-60 and BEL-7402 cells with IC_{50} values of 0.038 and 0.97 µM respectively.[58] Three new tetranorlabdane diterpenoids, asperolides A-C (**52-54**), and two related tetra norditerpenoid derivatives, wentilactones A and B (**55, 56**), were characterized from the culture extracts of *Aspergillus wentii* EN-48, derived from the marine brown alga *Sargassum* sp. All of them were evaluated for cytotoxic activity against HeLa, HepG2, MCF-7, MDA-MB-231, NCI-H460, SMMC-7721, and SW1990 cell lines with **56** being regarded as the most potent among the tested compounds (IC_{50} = 17 µM).[59] Three new macrocyclic epoxy-diterpenes were produced from an unidentified fungal strain (MPUC 046) derived from the marine brown alga *Ishige okamurae*. The isolated compounds show similarity to the known platelet activating factor (PAF) antagonists, phomactins, thats why they were named as phomactin I (**57**), 13-epi-phomactin I (**58**) and phomactin J (**59**).[60] (Table 3, Figure 2)

Nitrogenated compounds

Amines and amides:

Alternaria tenuis Sg17-1 was isolated from an unidentified alga (Zhoushan Island, China) and after the extraction of the culture broth of this fungus, a new isocoumarin (**60**) containing an atypical seven-membered ring in its side chain was discovered. Compound **60** exhibited in vitro cytotoxicity against human malignant A375-S2 and Hela cell lines with IC_{50} values of 0.3 and 0.05 mM respectively.[61] Methyl 4-(3,4-dihydroxybenzamido) butanoate (**61**), a novel benzamide derivative was isolated from the endophytic fungus *Aspergillus wentii* EN-48 derived from marine algae and showed significant DPPH free radical scavenging activity with an IC_{50} value of 23.1 µM.[62] Ten asperpyrone-type BNPs (**62-71**) were characterized from the fungus *Aspergillus niger*.

Table 2. Cytotoxic polyketides from marine aglae associated endophytic fungi.

Sl.	Host	Endophytes	Scientist	Compounds	Derivatives	Activities	Ref
1.	*Enteromorpha* sp.	*Coniothyrium cereale*	Elsebai *et al.*, 2011	Coniosclerodorolide (**1**), Sclerodine (**2**), Trypethelone (**3**), Coniosclerodin (**4**), Coniosclerolide (**5**), Cereolactam (**6**), Cereoaldomine (**7**)	Phenalenone derivatives	Cytotoxic and antimicrobial activities (**1-3**), Inhibitory activity on HLE (**4-7**)	36
2.	*Ceramium* sp.	*Phaeosphaeria Spartinae*	Elsebai *et al.*, 2010	Anofinic acid (**8**), Prenyl OH benzoic acid (**9**), Spartinoxide (**10**)		Inhibitory activity on HLE (**8**)	37
3.	*Carpopeltis cornea* red algae	*Aspergillus parasiticus*	Son *et al*., 2002	Parasitenone (**11**)	Gabosine derivative	Moderate free radical scavenging activity	38
4.	*Enteromorpha* sp.	*Wardomyces anomalus*	Abdel-Lateff *et al.*, 2003	Anomalin A (**12**)	Xanthone derivatives	Tyrosine kinase inhibitory & antioxidative activity	39
5.	*Sargassum fusiform* brown algae	*Aspergillus pseudodeflectus*	Ogawa *et al.*, 2004	Pseudodeflectusin (**14**)	Isochroman derivative	Selective cytotoxic activity against several human cancer cell lines including the stomach (NUGC-3), cervix (HeLa-S3), and peripheral blood (HL 60)	40
6.	*Actinotrichia fragilis*	*Cladosporium L037* species	Shigemori *et al*., 2004	Sporiolides A (**15**) and B (**16**)	12-membered macrolides	Potent cytotoxicity against murine lymphoma L1210 cells	41
7.	*Durvillaea Antarctica*	*Gliocladium* sp.	Lang *et al*., 2006	4-ketoclonostachydiol (**17**)	Macrodiolide	Strong cytotoxicity	42
8.	*Polysiphonia urceolata*	*Chaetomium globosum*	Wang *et al*., 2006b	Chaetopyranin (**18**)	Benzaldehyde derivative	Cytotoxic against human microvascular endothelial cells, hepatocellular carcinoma cells (SMMC-7721) and human lung epithelial cells	43
			Abdel-Lateff, 2008	Chaetominedione (**45**)	Benzonaphthyridinedione derivative	p56lck tyrosine kinase inhibitory activity	44
9.	Inner tissue of a marine green alga	*Monodictys putredinis*	Krick *et al*., 2007	Monodictysins A-C (**19-21**), Monodictyxanthone (**22**) Monodictyphenone (**23**)	Monomeric xanthones Benzophenone	Inhibition of cytochrome P450 1A (**20**), Induction of NAD(P)H:quinine reductase (QR) in cultured mouse	45
10.	*Acanthaphora spicifera*	*Curvularia* sp.	Greve *et al.*, 2008	Apralactone A (**24**), Antipodes of curvularin macrolides (**25-27**)	Macrolide	Cytotoxic towards human tumor cell lines	46
11	*Laurencia* sp.	*Penicillium chrysogenum*	Gao *et al.*, 2010	Penicitides A (**28**)	--	Moderate cytotoxic against the human hepatocellular liver carcinoma cell line	47
12	*Laurencia ceylanica*	*Aspergillus terreus*	Haroon *et al*., 2013	New butyrolactone (**30**)		Inhibition of β-glucuronidase	48
13	*Grateloupia turuturu*	*Paecilomyces variotii*	Zhang *et al.*, 2015a	Butyrolactone IX (**31**), Aspulvinone O (**32**)	Butenolide derivatives	DPPH radical scavenging activity (**32**)	49
14	*Halimeda copiosa*	*Aspergillus* sp.	Fenical *et al*., 2000	Halimide (**33**)	Alkaloid	Growth inhibition of colon and ovarian carcinoma cells	50

15	Unidentified algae	*Emericella nidulans var. acristata*	Kralj *et al*., 2006	Arugosin G (**34**), Arugosin H (**35**), Arugosin B (**36**), Arugosin A (**37**)	Prenylated polyketides	Cytotoxic toward tumor cell lines (**36, 37**)	16
16	Unidentified algae	*Monodictys putredinis*	Pontius *et al*., 2008b	Monodictyochromes A (**38**) and B (**39**)	Dimeric xanthone derivatives	Inhibit cytochrome P450 1A activity	52
17	Unidentified	*Nodulisporium* sp.	Pontius *et al*., 2008a	Noduliprevenone (**40**)	Heterodimeric chromanone	Inhibitor of P450 (CYP1A)	51
18	*Blidingia minima*	*Penicillium* sp.	Zhu *et al*., 2009	Citrinal A (**41**)	Tricyclic citrinin derivative	Cytotoxic effects on the A-549 and HL-60 cell lines	53
19	*Bostrychia tenella*	*Xylaria* sp.	de Felício *et al*., 2015	Cytochalasin D (**42**)	Alkaloid		54
20	*Polysiphonia violacea*	*Apiospora montagnei*	Klemke *et al*., 2004	Epiepoxydon (**43**)		Significant cytoxicity against human cancer cell lines.	14
21	*Ulva* sp.	*Ascochyta saliconiae*	Nagle *et al*., 2004	2, 3-dihydro-2-hydroxy-2, 4- dimethyl-5-trans-propenylfura-3-one (**44**)		Tyrosine kinase inhibitor	55

Table 3. Cytotoxic terpenoids from marine aglae associated endophytic fungi.

Sl.	Host	Endophytes	Scientist	Compounds	Derivatives	Activities	Ref
1.	*Enteromorpha* sp.	*Cadophora malorum SY3-1-1MIT*	Almeida *et al*., 2010	15-hydroxysclerosporin (**45**),12-hydroxysclerosporin (**46**),11-hydroxysclerosporin (**47**),8-hydroxy sclerosporin (**48**)	Hydroxylated sclerosporin derivatives	Fat-accumulation inhibitory activity against 3T3-L1murine adipocytes	56
2.	*Pestalotiopsis* sp. Z233	*Sargassum horneri*	Wu *et al*., 2013	1β,5α,6α,14-tetraacetoxy-9α-benzoyloxy-7β H-eudesman-2β,11-diol (**49**), 4α,5α-diacetoxy-9α-benzoyloxy-7βh-eudesman-1β,2β,11, 14-tetraol (**50**)	Eudesmane ses-quiterpenes	Tyrosinase inhibitory activities	57
3.	*Laurencia* sp.	*Penicillium chrysogenum QE N-24S*	Du *et al*., 2009	Conidiogenone C (**51**)	Diterpenes of cyclopiane class	Cytotoxic effect to HL-60	58
4.	*Sargassum* sp.	*Aspergillus wentii EN-48*	Sun *et al*., 2012	Asperolides A-C (**52-54**), Wentilactones A (**55**) and B (**56**)	Tetranorlabdane diterpenoids	Potent cytotoxic against a tumor cells (**56**)	59
5.	*Ishige okamurae*	Unidentified fungal strain (MPUC 046)	Ishino *et al*., 2010	Phomactin I (**57**), 13-epi-phomactin I (**58**), Phomactin J (**59**)	Diterpene	Platelet activating factor (PAF) antagonists	60
6.	Unidentified alga	*Alternaria tenuis*	Huang *et al*., 2006	Sg1714 (**44**)	A novel isocoumarin	Cytotoxicities in vitro against human malignant A375-S2	61
7.	---	*Aspergillus wentii*	Li *et al*., 2014	Methyl4-(3,4-dihydroxy benzamido) butanoate (**61**)	Benzamide derivative	Significant DPPH radical scavenging	62
8.	*Sargassum* sp.	*Aspergillus niger*	Fang *et al*., 2016	Aurasperone A (**62**), Fonsecinone D (**63**), Aurasperone F (**64**), Fonsecinone B (**65**), Aurasperone B (**66**), Aurasperone C (**67**), Fonsecinone A (**68**), Asperpyrone A (**69**), Fonsecinone C (**70**), Asperpyrone D (**71**)		Weak cytotoxicities (IC_{50}> 30 μm) against 10 human cancer cell lines (K562, A549, Du145, H1975, MCF-7, Huh-7, HL7702, HL60, HeLa, and Molt-4).	63
9.	*Codium fragile.*	*Gibberella zeae*	Liu *et al*., 2011	3-hydroxy-5-(hydroxymethyl)-4-(4'-hydroxyphenoxy) pyrrolidin-2-one (**72**)	Pyrrolidine derivative	Cytotoxicity against A-549 and BEL-7402 cell lines.	64

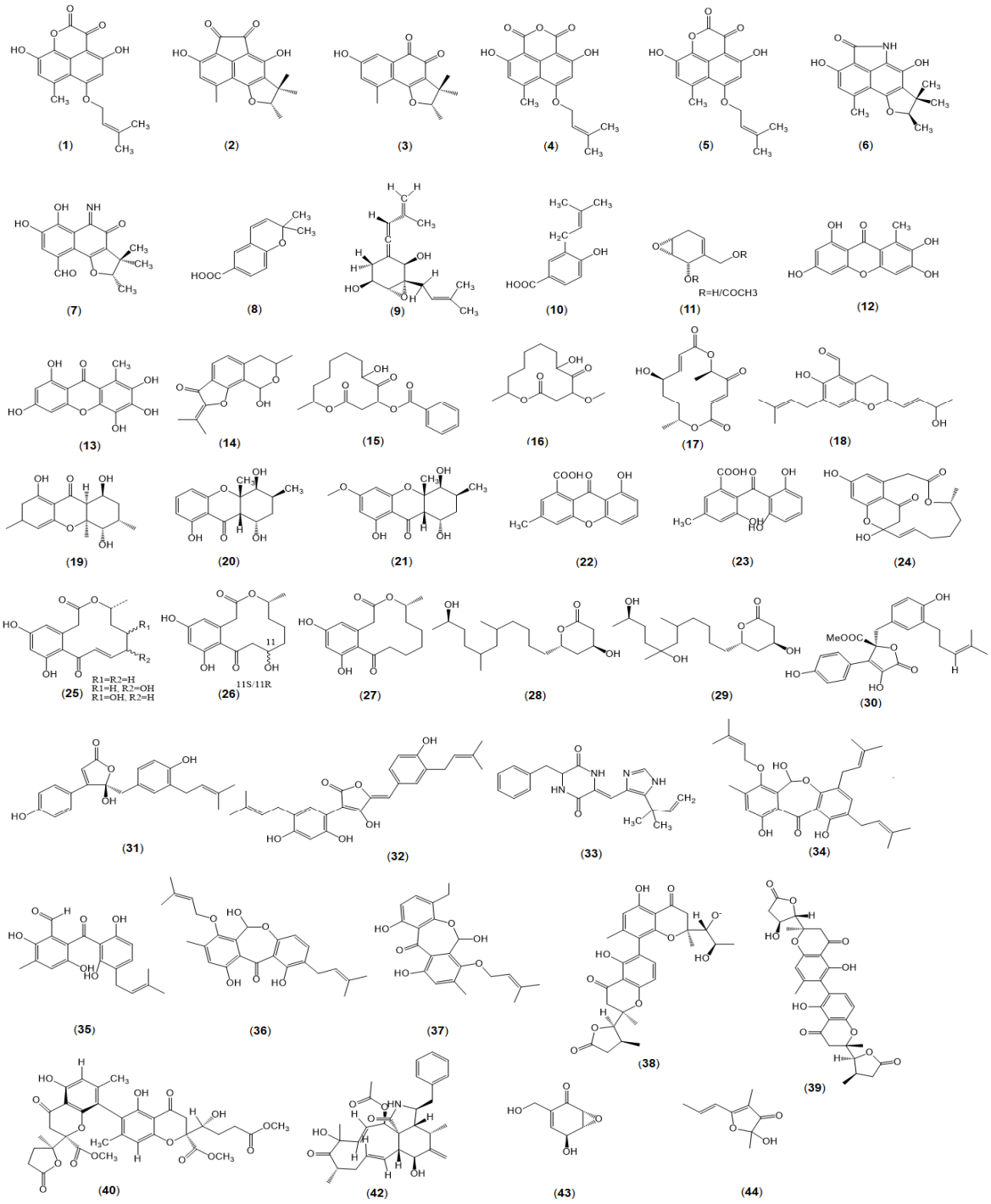

Figure 1. Cytotoxic polyketidesfrom marine aglae associated endophytic fungi.

SCSIO Jcsw6F30, derived from a marine alga *Sargassum* sp. All of the BNPs were found as weak cytotoxic compounds against 10 human tumor cells (IC_{50}> 30 μM). Besides, three of them, aurasperone F (**62**), aurasperone C (**63**) and asperpyrone A (**64**), showed obvious COX-2–inhibitory activities, with

the IC_{50} values of 11.1, 4.2 and 6.4 µM respectively.[63] 3-hydroxy-5-(hydroxymethyl)-4-(4' hydroxyphenoxy) pyrrolidin-2-one (**72**), a new pyrrolidine derivative was identified from the culture extracts of an endophytic fungus *Gibberella zeae*, obtained from the marine green alga *Codium fragile* and showed cytotoxic activity against A-549 and BEL-7402 cell lines.[64] All the amines and amides with cytotoxic potentials are are summarized in table 4 and the structures are given in figure 3.

Table 4. Cytotoxic nitrogenated compounds from marine aglae associated endophytic fungi.

Sl.	Host	Endophytes	Scientist	Compounds	Derivatives	Activities	Ref
1	*Valonia utricularis*	*Chaetomium* sp.	Abdel-Lateff, 2008	Chaetominedione (**73**)	Benzonaphthyridinedione	Potent tyrosine kinase inhibitor	44
2	*Sargassum kjellmanianum*	*Aspergillus ochraceus*	Cui *et al.*, 2009	2-hydroxy circumdatin C (**74**)	Benzodiazepine alkaloids	Exhibited significant dpph radical scavenging activity	65
3	*Grateloupia turuturu*	*Paecilomyces variotii EN-291*	Zhang *et al.*, 2015b	Varioloid A (**75**) & B (**76**)	Diketopiperazine type alkaloid	Compounds 77 and 78 exhibited cytotoxicity against A549, HCT116, and hepg2 cell lines, with IC_{50} values ranging from 2.6 to 8.2 µg/ml.	108
4	*Actinotrichia fragilis*	*Penicillium citrinum N-059*	Tsuda *et al.*, 2004	Citrinadin A (**77**)	Pentacyclic spiroindolinone alkaloid	Cytotoxicity against L1210 and KB cell lines	67
			Mugishima *et al.*, 2005	Citrinadin B (**78**)	Pentacyclic indolinone alkaloid	Modest cytotoxicity against l1210 cells	68
5	*Enteromorpha tubulosa*	*Aspergillus flavus* C-F-3	Lin *et al.*, 2009	Iso-α-Cyclo-piazonic acid (**79**)		Cytotoxic to several human tumor cell lines (HL-60,MOLT-4,A-549,andbel-7402 cell lines)	69
6	*Sargassum* sp.	*Aspergillus* sp. SpD081030G1f1	Izumikawa *et al.*, 2010	JBIR-81 (**80**) and JBIR-82 (**81**)	Terpeptin analogues	Radical scavengers due to their protective effect against L-glutamate toxicity	70
7	*Ulva pertusa*	*Chaetomium globosum*	Cui *et al.*, 2010a	Cyto-globosins A–G (**82-88**)	Cytochalasans	Cytotoxic activity against the a-549 tumor cell line	71
8	*Enteromorpha* sp.	*Coniothyrium cereal*	Elsebai *et al.*, 2012	Conioimide (**89**)	Isoindole pseudoalkaloid	Selective inhibition of human leukocyte elastase	72
9	*Sargassum tortile*	*Leptosphaeria* sp.	Takahashi *et al.*, 1994	Lep F (**91**) and C (**92**)	Leptosin	Strong growth-inhibiting and apoptosis-inducing activities against human lymphoblastoid RPMI8402 cells and human embryonic kidney cell line 293 cells	73
10	*Avrainvillea* sp.	*Fusarium* sp. CNL-619	Cueto *et al.*, 2000	N-methyl-sansalvamide (**93**)	Cyclic depsipeptide	Weak in vitro cytotoxicity in the NCI human tumor cell line	75
10.	*Lomentaria catenate*	*Aspergillus* sp.	Li *et al*., 2004	Golmaenone (**94**)	Diketopiperazine alkaloid	Significant radical scavenging and UV-A protecting properties	76
11.	*Ceradiction spongiosum*	Unidentified	Komatsu *et al.*, 2001	Dictyonamides A (**95**)	Peptides	Inhibited cyclin-dependent kinase 4	77

Table 5. Cytotoxic steroids from marine aglae associated endophytic fungi.

Sl.	Host	Endophytes	Scientist	Compounds	Derivatives	Activities	Ref
1.	*Phaeosphaeria spartinae*	*Ceramium* sp.	Elsebai *et al.*, 2013	Spartopregnenolone (**97**)	4α-carboxylic pregnane-derivative	Steroidal	78
2.	*Sargassum kjellmanianum*	*Aspergillus ochraceus EN-31*	Cui *et al.*, 2010b	7-Nor-ergosterolide, (**98**) 3β-hydroxyergosta-8, 4(28)-dien-7-one (**99**)	7-norsteroid	Cytotoxicity against NCI-H460,SMMC-7721,and SW 1990 cell lines	79
3.	*Corallina officinalis*	*Aspergillus flavus Cf-5*	Qiao *et al.*, 2011	3β,4α-dihydroxy-26-methoxyergosta-7,24(28)-dien-6-one		Low inhibition of acetylcholinesterase (AChE)	18

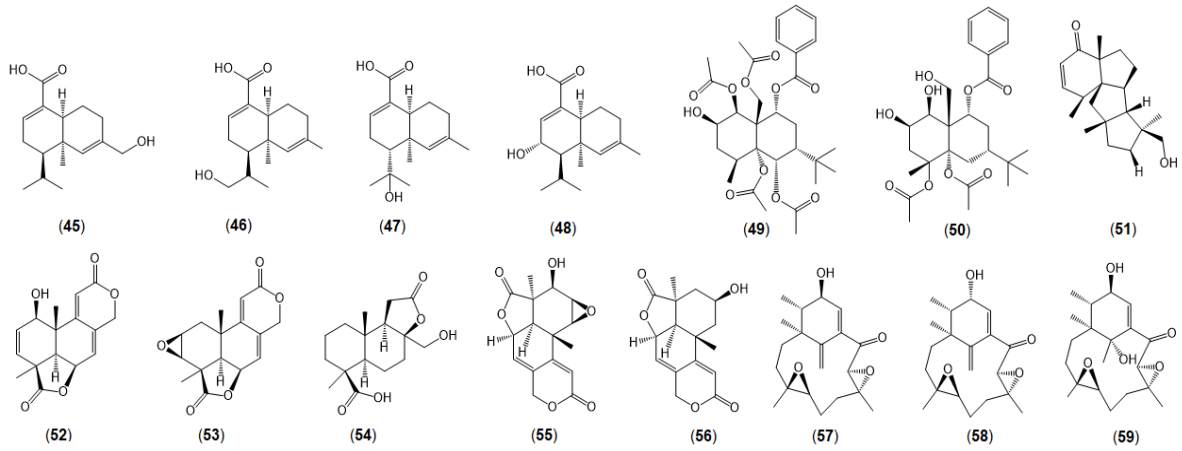

Figure 2. Cytotoxic terpenoids from marine algae associated endophytic fungi.

Quinolines and quinazoline derivatives:

From a culture of *Chaetomium* sp. Az 3-10 obtained from the marine alga *Valonia utricularis* (Azores, Atlantic Ocean) chaetominedione (**73**), a new benzonaphthyridinedione derivative was characterized which showed significant tyrosine kinase inhibitory activity.[64] The endophytic fungus *Aspergillus ochraceus*, obtained from the marine brown alga *Sargassum kjellmanianum* produced a novel benzodiazepine analogue, 2-hydroxycircumdatin C (**74**) in its culture. The culture extracts also provide another compound (11aS)-2,3-dihydro-7-methoxy-1H-pyrrolo[2,1 c] [1,4] benzodiazepine-5,11(10H,11aH)-dione, which has been identified from a natural resource for the first time, but has been synthesized previously, along with five structurally related known alkaloids. Compound **74** showed potent DPPH free radical scavenging activity and an IC_{50} value of 9.9 µM, which is 8.9-fold more potent than that of butylated hydroxytoluene (BHT), a well-known synthetic positive control.[65] Varioloid A (**75**), a new indolyl-6,10b-dihydro-5a*H*-[1]benzofuro[2,3-*b*]indole derivative, and another similar compound varioloid B (**76**), was characterized from the endophytic fungus *Paecilomyces variotii* EN-291 derived from an unidentified marine alga.[66](Table 4, Figure 3)

Indole derivatives:

Citrinadin A (**77**), a novel pentacyclic spiroindolinone alkaloid, was isolated from the endophytic fungus *Penicillium citrinum* N-059, derived from marine red alga *Actinotrichia fragilis* (Hedo Cape, Okinawa Island) and showed moderate cytotoxic activity against L1210 and KB cell lines (with IC_{50} values of 9.9 and 16.0 µM respectively).[67] The same fungus also provided a new congener, citrinadin B (**78**), having moderate cytotoxicity against L1210 cells (with an IC_{50} value of 20.8 µM).[68] The fungus *Aspergillus flavus* C-F-3, obtained

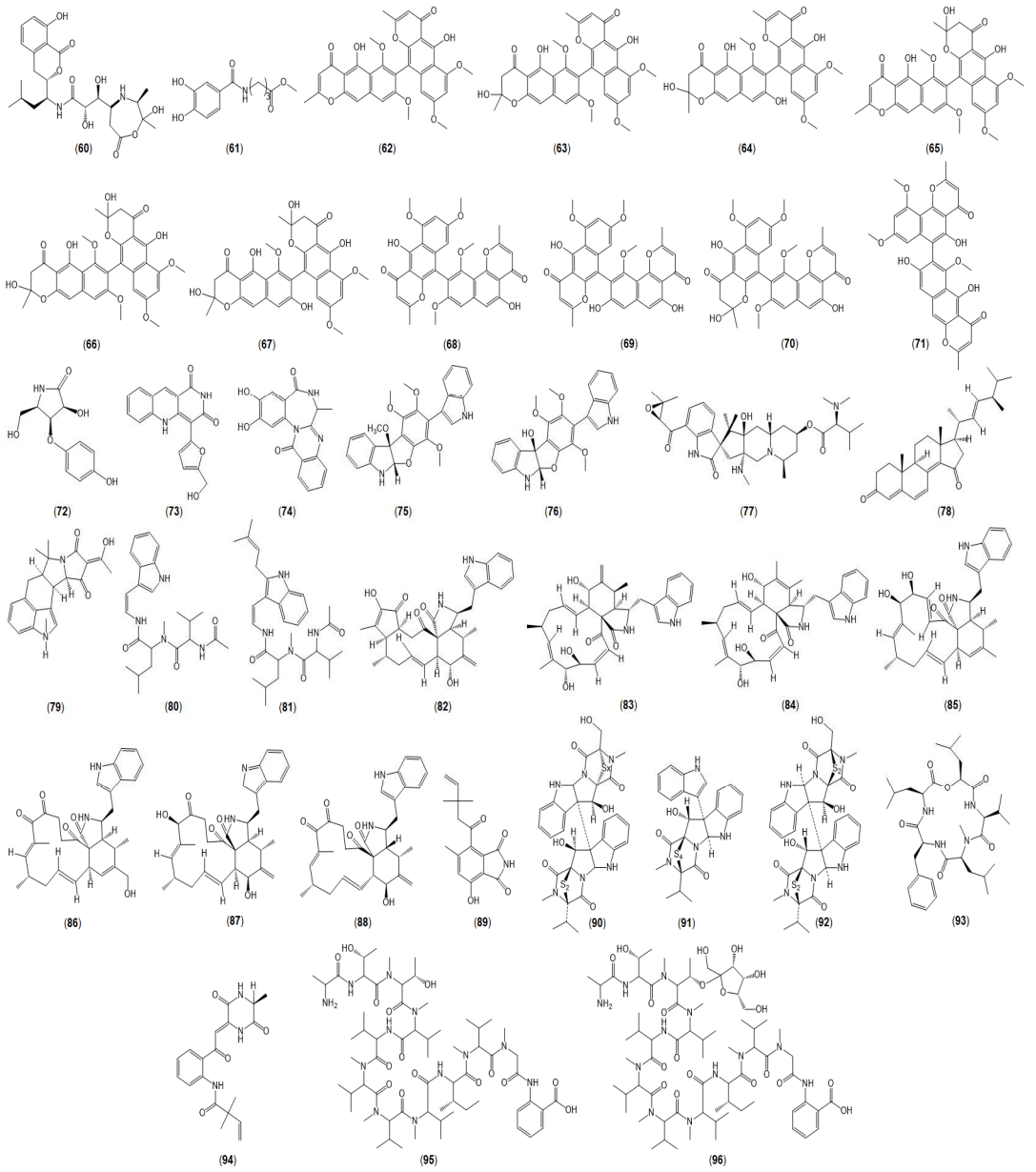

Figure 3. Cytotoxic nitrogenated compounds from marine aglae associated endophytic fungi.

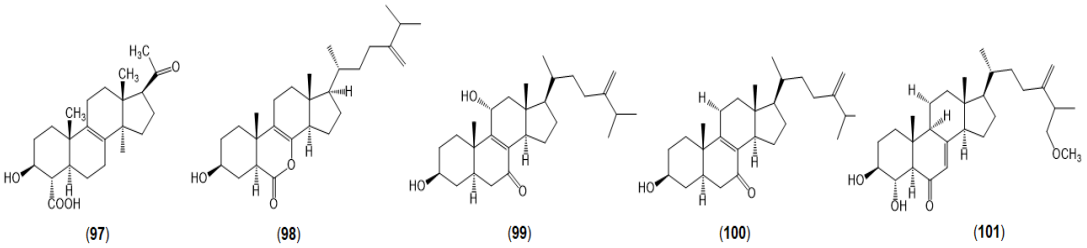

Figure 4. Cytotoxic steroids from marine algae associated endophytic fungi.

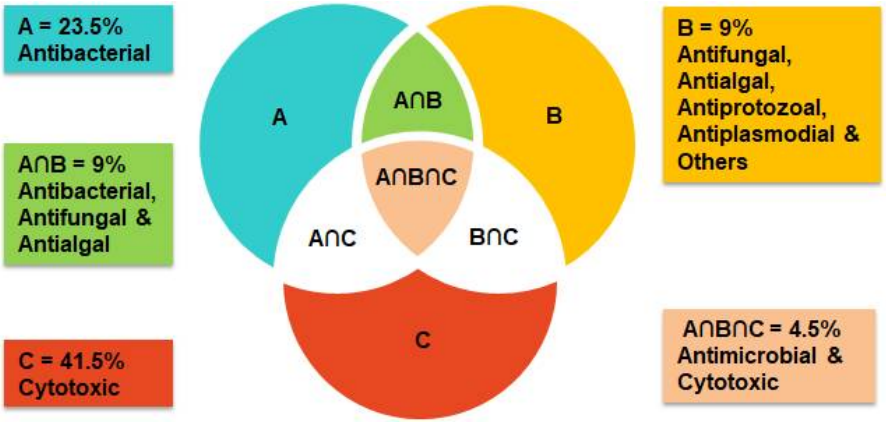

Figure 5. Different classes of bioactive compounds isolated from marine algicolous endophytic fungi upto 2017 (No compound has fallen into A∩C & B∩C groups).

from green alga *Enteromorpha tubulosa* (Putian Pinghai, China), is the source of a moderate cytotoxic compound iso-α-cyclopiazonic acid (**79**), having activity against several human tumor cell lines (HL 60, MOLT- 4, A-549, and BEL-7402 cell lines).[69] Two novel fungus-derived terpeptin analogues, namely JBIR-81 (**80**) and JBIR-82 (**81**), were found as potent free radical scavengers because of their inhibitory activities against L-glutamate toxicity (with EC_{50} values of 0.7 and 1.5 µM), were isolated from an *Aspergillus* sp. SpD081030G1f1 obtained from the brown alga *Sargassum* sp. (Ishigaki Island, Okinawa Prefecture, Japan)[70]. Seven novel cytochalasan derivatives were isolated from the culture of an endophytic fungus *Chaetomium globosum* QEN-14, obtained from the marine green alga *Ulva pertusa* (Qingdao coastline, China), which were named as Cytoglobosins A–G (**82-88**). Among those, cytoglobosins C and D showed cytotoxicity against the A-549 tumor cell line (IC_{50} values of 2.26 and 2.55 µM respectively).[71] The endophyte *Coniothyrium cereale* of the green alga *Enteromorpha* sp. provided the isoindole pseudoalkaloid conioimide (**89**) from its culture. The compound **89** showed selective inhibitory activity against human leukocyte elastase.[72] Epipolysulfanyl-dioxopiperazines (**90**), a member of the family of leptosins, was produced from the cultured mycelia of the endophytic fungus *Leptosphaeria* sp. obtained from the brown alga *Sargasssum tortile.* Leptosin A (**90**) showed cytotoxic activity against P-388 leukemia cells through inhibition of topoisomerase II.[73] Leps F and C (**91, 92**) were also found from same fungal species. These isolated metabolites exhibited significant growth-inhibition and apoptosis-induction of human lymphoblastoid RPMI8402 cells and human embryonic kidney cell line 293 cells. Furthermore, leps F and C also have inhibitory activity in the survival pathway by inactivating (i.e. through dephosphorylation) Akt/protein kinase B enzyme.[74] The sources of cytotoxic endophytes and the structures of some important indole derivatives are summarized in Table 4 and Figure 3, respectively.

Peptides:

Few peptides with cytotoxic activities from marine associated algicolous endophytes are also reported (Table 4, Figure 3). A novel cyclic depsipeptide, N-methylsansalvamide (**93**), was isolated from the culture of an endophyte *Fusarium* sp. CNL-619, derived from the green alga *Avrainvillea* sp. (Bovoni Cay, United States Virgin Islands). The compound **93** showed weak cytotoxic activity against NCI human tumor cell line with a GI_{50} value of 8.3 µM.[75] Golmaenone (**94**), a diketopiperazine alkaloid, was found as a potent free radical scavenger (with an IC_{50} value of 20 µM) and UV-A protector (with an ED_{50} value of 90 µM) from the culture extracts of an *Aspergillus* species (# MFA 212) obtained from a red alga *Lomentaria catenata*

(Golmae Village, Ulsan City, Korea).[76] Investigations of an unknown fungus separated from the red alga *Ceradictyon spongiosum* (Seragaki Beach, Okinawa) led to the identification of two metabolites, dictyonamides A (**95**) and B (**96**) of linear dodecapeptide class. Dictyonamide A showed inhibitory activity against cyclin-dependent kinase 4 enzyme (with an IC_{50} value of 13.0 µM), whereas dictyonamide B showed inactivity (IC_{50} value > 30 µM).[77]

Steroids

A compound named spartopregnenolone (**97**) was isolated from an endophytic fungus *Phaeosphaeria spartinae* of the marine red alga *Ceramium* sp. having cytotoxic activity.[78] 7-Nor-ergosterolide (**98**), a rare 7-norsteroid with an uncommon pentalactone B-ring system, along with two related derivatives, 3β,11α-dihydroxyergosta-8,24(28)-dien-7-one **(99)** and 3β hydroxyergosta-8,24(28)-dien-7-one (**100**), were isolated from the endophyte *Aspergillus ochraceus* EN-31, obtained from the marine brown alga *Sargassum kjellmanianum* (Dalian coastline, China). Compounds **98** and **100** were found for the first time from an *Aspergillus* sp., however, these were previously reported from a *Penicillium* sp. The compound **98** showed cytotoxic activity against NCI-H460, SMMC-7721 and SW1990 cell lines with IC_{50} values of 12.1, 16.9 and 67.6 µM respectively.[79] Investigation of the endophyte *Aspergillus flavus* cf-5 of the marine red alga *Corallina officinalis* (Yantai, China), led to the isolation of a novel steroid (**101**) from its culture extracts. Compound **101** showed mild inhibitory activity against acetylcholinesterase (AChE) enzyme.[18] The sources of endophytes and the structures of steroids isolated from them are given in Table 5 and Figure 4, respectively.

CONCLUSION

Algicolous fungi studied up until now produce both structurally and functionally diverse compounds including steroids, alkaloids, tannins, terpenoids, phenolic acids, quinines, xanthones exhibiting anticancer, antimicrobial, antidiabetic, antioxidant, immunosuppressant and many more properties. In this review we have summarized and explored the possibility of marine algicolous endophytic fungi as a potential source of cytotoxic compounds. Venn diagram analysis (Figure 5) on the isolated compounds, showed that among all the reported cytotoxic and antimicrobial metabolites 41.5% metabolited were reported to have cytotoxic properties, 23.5% metabolites were reported to have antibacterial activities. In common, only 9% of the isolated metabolites showed antibacterial, antifungal and antialgal activities together, while other 9% were reported to have antifungal, antialgal, antiprotozoal, antiplasmodial and other activities. Among the reported metabolites in this review only 4.5% have both antimicrobial and cytotoxic effects. This analasys further indicated the importance of marine algicolous endophytic fungi as promising source for future anticancer drug discovery. However, most of this treasure is yet to be discovered. Until now, there is also lack of effective and efficient techniques to isolate potential strains. On the other hand, we often consider only the faster growing culturable strain of endophyties, but ignore the slow growing and unculturable strains. This might be a flaw in the endophytic research because such slow growing strains might have potential to produce high value metabolites. Hence, optimum fermentation conditions including media selection, different culture conditions, etc. are required to adjust considering the physiological and genetic scenario of endophytes. This might stimulate tranquil gene clusters responsible for secondary metabolism. Though many metabolites of endophytic fungi showed prospective bioactivities, but some of them were found inactive or showed weak activities in current reports. This was probably due to bias in the screening program. So, more effective and sensitive high-throughput screening models are strongly recommended for the search of potent cytotoxic metabolites. Particularly computer-aided virtual screening models can play a great role in exploring leads.

REFERENCES

1. Tan, R.X. and Zou, W.X. 2001. Endophytes: a rich source of functional metabolites. *Nat. Prod. Rep.* **18**, 448-459.
2. Stone, J.K., Bacon C.W. and White, J.F. 2000. An overview of endophytic microbes: endophytism defined. In: Microbial endophytes (Bacon, C.W. and White, J.F., Eds.), Dekker, New York, pp. 330.
3. Schulz, B. and Boyle, C. 2006. What are endophytes? In: Microbial root endophytes (Schulz, B., Boyle, C. and Sieber, T.N., Eds.), Springer, Berlin, pp. 113.
4. Rodriguez, R.J., White, J.F., Arnold, A.E. and Redman, R.S. 2009. Fungal endophytes: diversity and functional roles. *New Phytol.* **182**, 314–330. doi:10.1111/j.14698137.2009.02773.x
5. Strobel, G.A. 2002. Rainforest endophytes and bioactive products. *Crit. Rev. Biotechnol.* **22**, 315-333. doi:10.1080/07388550290789531
6. Arnold, A.E., Maynard, Z., Gilbert, G.S., Coley, P.D. and Kursar, T.A. 2000. Are tropical fungal endophytes hyperdiverse? *Ecol. Lett.* **3**, 267-274.
7. Schulz, B., Boyle, C. and Draeger, S. 2002. Endophytic fungi: A source of biologically active secondary metabolites. *Mycol. Res.* **106**, 996-1004.
8. Hollants, J., Leliaert, F., De Clerck, O. and Willems, A. 2010. How endo is endo?: surface sterilization of delicate samples: a Bryopsis (Bryopsidales, Chlorophyta) case study. *Symbiosis.* **51**, 131-138.
9. Strobel, G. and Daisy, B. 2003. Bioprospecting for microbial endophytes and their natural products. *Microbiol. Mol. Biol. Rev.* **67**, 491-502. doi:10.1128/MMBR.67.4.491502.2003
10. Strobel, G.A. 2003. Endophytes as sources of bioactive products. *Microbes Infect.* **5**, 535-544.
11. Strobel, G., Yang, X., Sears, J., Kramer, R., Sidhu, R.S. and Hess, W.M. 1996. Taxol from *Pestalotiopsis microspora*, an endophytic fungus of *Taxus wallachiana*. *Microbiology. (Reading, Engl.)* **142** (Pt 2), 435-440.
12. Bacon, C.W. and White, J.F. 1994. Stain, media and procedure for analyzing endophytes. In: Biotechnology of endophytic fungi of grasses (Bacon, C.W. and White, J.F., Eds.), CRC Press, Boca Raton, pp. 47-56.
13. Kjer, J., Debbab, A., Aly, A.H. and Proksch, P. 2010a. Methods for isolation of marine derived endophytic fungi and their bioactive secondary products. *Nat. Protoc.* **5**, 479-490. doi:10.1038/nprot.2009.233
14. Klemke, C., Kehraus, S., Wright, A.D. and König, G.M. 2004. New secondary metabolites from the marine endophytic fungus *Apiospora montagnei*. *J. Nat. Prod.* **67**, 1058-1063. doi:10.1021/np034061x
15. Schulz, B., Draeger, S., Dela, C.T.E., Rheinheimer, J., Siems, K., Loesgen, S., Bitzer, J., Schloerke, O., Zeeck, A., Kock, I., Hussain, H., Dai, J. and Krohn, K. 2008. Screening strategies for obtaining novel, biologically active, fungal secondary metabolites from marine habitats. *Botanica Marina*. **51**, 219-234. doi:10.1515/BOT.2008.029
16. Kralj, A., Kehraus, S., Krick, A., Eguereva, E., Kelter, G., Maurer, M., Wortmann, A., Fiebig, H.H. and König, G.M. 2006. Arugosins G and H: prenylated polyketides from the marine derived fungus *Emericella nidulans* var. *acristata*. *J. Nat. Prod*. **69**, 995-1000. doi:10.1021/np050454f
17. Naganuma, M., Nishida, M., Kuramochi, K., Sugawara, F., Yoshida, H. and Mizushina, Y. 2008. 1-deoxyrubralactone, a novel specific inhibitor of families X and Y of eukaryotic DNA polymerases from a fungal strain derived from sea algae. *Bioorg. Med. Chem.* **16**, 2939-2944. doi:10.1016/j.bmc.2007.12.044
18. Qiao, M.F., Ji, N.Y., Miao, F.P. and Yin, X.L. 2011. Steroids and an oxylipin from an algicolous isolate of *Aspergillus flavus*. *Magn. Reson. Chem.* **49**, 366-369.
19. Erbert, C., Lopes, A.A., Yokoya, N.S., Furtado, N.A.J.C., Conti, R., Pupo, M.T., Lopes, J.L.C. and Debonsi, H.M. 2012. Antibacterial compound from the endophytic fungus *Phomopsis longicolla* isolated from the tropical red seaweed *Bostrychia radicans*. *Botanica Marina.* **55**, 435-440. doi:10.1515/bot20110023
20. Strobel, G., Stierle, A., Stierle D. and Hess, W.M. 1993. Taxomyces andreanaea proposed new taxon for a bulbilliferous hyphomycete associated with Pacific yew. *Mycotaxon.* **47**: 71-78.
21. Lee, J.C., Strobel, G.A., Lobkovsky, E. and Clardy, J. 1996. Torreyanic acid: a selectively cytotoxic quinone dimer from the endophytic fungus *Pestalotiopsis microspora*. *J. Org. Chem.* **61**, 3232-3233. doi:10.1021/jo960471x
22. Weber, R.W.S., Stenger, E., Meffert, A. and Hahn, M. 2004. Brefeldin: a production by *Phoma medicaginis* in dead precolonized plant tissue: a strategy for habitat conquest? *Mycol. Res.* **108**, 662-671.
23. Korkina, L.G. 2007. Phenylpropanoids as naturally occurring antioxidants: from plant defense to human health. *Cell. Mol. Biol.* (*Noisylegrand*) **53**, 15-25.
24. Strobel, G., Miller, R.V., Miller, C., Condron, M., Teplow, D.B. and Hess WM. 1999b. Cryptocandin, a potent antimycotic from the endophytic fungus *Cryptosporiopsis* cf. *quercina*. *Microbiology*. **145**, 1919-1926.
25. Li, J.Y., Harper, J.K., Grant, D.M., Tombe, B.O., Bashyal, B., Hess, W.M. and Strobel, G.A. 2001. Ambuic acid, a highly functionalized cyclohexenone with antifungal activity from *Pestalotiopsis* sp. and *Monochaetia* sp. *Phytochemistry*. **56**, 463-468.
26. Li, J.Y. and Strobel, G.A. 2001. Jesterone and hydroxyjesteroneantioomycete cyclohexenone epoxides from the endophytic fungus *Pestalotiopsis jesteri*. *Phytochemistry*. **57**, 261-265.
27. Li, E., Jiang, L., Guo, L., Zhang, H. and Che, Y. 2008a. Pestalachlorides AC, antifungal metabolites from the plant endophytic fungus *Pestalotiopsis adusta*. *Bioorg. Med. Chem.* **16**, 7894-7899.
28. Hormazabal, E., Astudillo, L., Schmeda Hirschmann, G., Rodríguez, J. and Theoduloz, C. 2005. Metabolites from *Microsphaeropsis olivacea*, an endophytic fungus of *Pilgerodendron uviferum*. *Z. Naturforsch.* **60**, 11–21. doi:10.1515/znc20051203

29. Guo, B., Dai, J.R., Ng, S., Huang, Y., Leong, C., Ong, W. and Carté, B.K. 2000. Cytonic acids A and B: novel tridepside inhibitors of hCMV protease from the endophytic fungus *Cytonaema* species. *J. Nat. Prod.* **63**, 602-604.

30. Pittayakhajonwut, P., Suvannakad, R., Thienhirun, S., Prabpai, S., Kongsaeree, P. and Tanticharoen, M. 2005. An anti-herpes simplex virustype 1 agent from *Xylaria mellisii* (BCC 1005). *Tetrahedron Lett.* **46**, 1341-1344. doi:10.1016/j.tetlet.2004.12.110

31. Singh, S.B., Ondeyka, J.G., Tsipouras, N., Ruby, C., Sardana, V., Schulman, M., Sanchez, M., Pelaez, F., Stahlhut, M.W., Munshi, S., Olsen, D.B. and Lingham, R.B. 2004. Hinnuliquinone, a C-2symmetric dimeric nonpeptide fungal metabolite inhibitor of HIV1 protease. *Biochem. Biophys. Res. Commun*. **324**, 108-113. doi:10.1016/j.bbrc.2004.08.234

32. Zhang, B., Salituro, G., Szalkowski, D., Li, Z., Zhang, Y., Royo, I., Vilella, D., Díez, M.T., Pelaez, F., Ruby, C., Kendall, R.L., Mao, X., Griffin, P., Calaycay, J., Zierath, J.R., Heck, J.V., Smith, R.G. and Moller, D.E. 1999. Discovery of a small molecule insulin mimetic with antidiabetic activity in mice. *Science*. **284**, 974-977.

33. Salituro, G.M., Pelaez, F. and Zhang, B.B. 2001. Discovery of a small molecule insulin receptor activator. *Recent Prog. Horm. Res*. **56**, 107-126.

34. Strobel, G., Ford, E., Worapong, J., Harper, J.K., Arif, A.M., Grant, D.M., Fung, P.C.W. and Ming Wah Chau, R. 2002. Isopestacin, an isobenzofuranone from *Pestalotiopsis microspora*, possessing antifungal and antioxidant activities. *Phytochemistry*. **60**, 179-183.

35. Ren, Y., Strobel, G.A., Graff, J.C., Jutila, M., Park, S.G., Gosh, S., Teplow, D., Condron, M., Pang, E., Hess, W.M. and Moore, E. 2008. Colutellin A, an immunosuppressive peptide from *Colletotrichum dematium*. *Microbiology. (Reading, Engl.)* **154**, 1973-1979.

36. Elsebai, M.F., Kehraus, S., Lindequist, U., Sasse, F., Shaaban, S., Gütschow, M., Josten, M., Sahl, H.G. and König, G.M. 2011. Antimicrobial phenalenone derivatives from the marine derived fungus *Coniothyrium cereale*. *Org. Biomol. Chem*. **9**, 802-808. doi:10.1039/c0ob00625d

37. Elsebai, M.F., Kehraus, S., Gütschow, M. and König, G.M. 2010. Spartinoxide, a new enantiomer of A82775C with inhibitory activity toward HLE from the marine derived fungus *Phaeosphaeria spartinae*. *Nat. Prod. Commun*. **5**, 1071-1076.

38. Son, B.W., Choi, J.S., Kim, J.C., Nam, K.W., Kim, D.S., Chung, H.Y., Kang, J.S. and Choi, H.D. 2002. Parasitenone, a new epoxycyclohexenone related to gabosine from the marine derived fungus *Aspergillus parasiticus*. *J. Nat. Prod*. **65**, 794-795.

39. Abdel-Lateff, A., Klemke, C., König, G.M. and Wright, A.D. 2003. Two new xanthone derivatives from the algicolous marine fungus *Wardomyces anomalus*. *J. Nat. Prod*. **66**, 706-708. doi:10.1021/np020518b

40. Ogawa, A., Murakami, C., Kamisuki, S., Kuriyama, I., Yoshida, H., Sugawara, F. and Mizushina, Y. 2004. Pseudodeflectusin, a novel isochroman derivative from *Aspergillus pseudodeflectus* a parasite of the sea weed, *Sargassum fusiform*, as a selective human cancer cytotoxin. *Bioorg. Med. Chem. Lett*. **14**, 3539-3543.

41. Shigemori, H., Kasai, Y., Komatsu, K., Tsuda, M., Mikami, Y. and Kobayashi, J. 2004. Sporiolides A and B, new cytotoxic twelve membered macrolides from a marine derived fungus *Cladosporium* species. *Mar. Drugs*. **2**, 164-169.

42. Lang, G., Mitova, M.I., Ellis, G., van der Sar, S., Phipps, R.K., Blunt, J.W., Cummings, N.J., Cole, A.L.J. and Munro, M.H.G. 2006. Bioactivity profiling using HPLC/microtiterplate analysis: application to a New Zealand marine alga derived fungus, *Gliocladium* sp. *J. Nat. Prod*. **69**, 621-624. doi:10.1021/np0504917

43. Wang, S., Li, X.M., Teuscher, F., Li, D.L., Diesel, A., Ebel, R., Proksch, P. and Wang, B.G. 2006b. Chaetopyranin, a benzaldehyde derivative, and other related metabolites from *Chaetomium globosum*, an endophytic fungus derived from the marine red alga *Polysiphonia urceolata*. *J. Nat. Prod*. **69**, 1622-1625. doi:10.1021/np060248n

44. Abdel-Lateff, A. 2008. Chaetominedione, a new tyrosine kinase inhibitor isolated from the algicolous marine fungus *Chaetomium* sp. *Tetrahedron Lett.* **49**, 6398-6400. doi:10.1016/j.tetlet.2008.08.064

45. Krick, A., Kehraus, S., Gerhäuser, C., Klimo, K., Nieger, M., Maier, A., Fiebig, H.H., Atodiresei, I., Raabe, G., Fleischhauer, J. and König, G.M. 2007. Potential cancer chemopreventive in vitro activities of monomeric xanthone derivatives from the marine algicolous fungus *Monodictys putredinis*. *J. Nat. Prod*. **70**, 353-360.

46. Greve, H., Schupp, P.J., Eguereva, E., Kehraus, S., Kelter, G., Maier, A., Fiebig, H.H. and König, G.M. 2008. Apralactone A and a new stereochemical class of curvularins from the marine derived fungus *Curvularia* sp. *Eur. J. Org. Chem*. **2008**. doi:10.1002/ejoc.200800522

47. Gao, S.S., Li, X.M., Du, F.Y., Li, C.S., Proksch, P. and Wang, B.G. 2010. Secondary metabolites from a marine derived endophytic fungus *Penicillium chrysogenum* QEN24S. *Mar. Drugs*. **9**, 59-70. doi:10.3390/md9010059

48. Haroon, M.H., Premaratne, S.R., Choudhry, M.I. and Dharmaratne, H.R.W. 2013. A new β-glucuronidase inhibiting butyrolactone from the marine endophytic fungus *Aspergillus terreus*. *Nat. Prod. Res*. **27**, 1060-1066. doi:10.1080/14786419.2012.708659

49. Zhang, P., Li, X.M., Wang, J.N., Li, X. and Wang, B.G. 2015a. New butenolide derivatives from the marine derived fungus *Paecilomyces variotii* with DPPH radical scavenging activity. *Phytochem. Lett*. **11**, 85-88.

50. Frenz, J.L., Kohl, A.C. and Kerr, R.G. 2004. Marine natural products as therapeutic agents: part 2. *Expert Opin. Ther. Pat*. **14**, 17-33. doi:10.1517/13543776.14.1.17

51. Pontius, A., Krick, A., Kehraus, S., Foegen, S.E., Müller, M., Klimo, K., Gerhäuser, C. and König, G.M. 2008a. Noduliprevenone: a novel heterodimeric chromanone with cancer chemopreventive potential. *Chemistry*. **14**, 9860-9863. doi:10.1002/chem.200801574
52. Pontius, A., Krick, A., Mesry, R., Kehraus, S., Foegen, S.E., Müller, M., Klimo, K., Gerhäuser, C. and König, G.M. 2008b. Monodictyochromes A and B, dimeric xanthone derivatives from the marine algicolous fungus *Monodictys putredinis*. *J. Nat. Prod*. **71**, 1793-1799. doi:10.1021/np800392w
53. Zhu, T.J., Du, L., Hao, P.F., Lin, Z.J. and Gu, Q.Q. 2009. Citrinal A, a novel tricyclic derivative of citrinin, from an algicolous fungus *Penicillium* sp. i11. *Chin. Chem. Lett.* **20**, 917-920. doi:10.1016/j.cclet.2009.03.009
54. de Felício, R., Pavão, G.B., de Oliveira, A.L.L., Erbert, C., Conti, R., Pupo, M.T., Furtado, N.A.J.C., Ferreira, E.G., Costa Lotufo, L.V., Young, M.C.M., Yokoya, N.S. and Debonsi, H.M. 2015. Antibacterial, antifungal and cytotoxic activities exhibited by endophytic fungi from the Brazilian marine red alga *Bostrychia tenella* (Ceramiales). *Rev. Bras. Farmacogn.* **25**, 641-650. doi:10.1016/j.bjp.2015.08.003
55. Nagle, D.G., Zhou, Y.-D., Mora, F.D., Mohammed, K.A. and Kim, Y.-P. 2004. Mechanism targeted discovery of antitumor marine natural products. *Curr. Med. Chem.* **11**, 1725-1756.
56. Almeida, C., Eguereva, E., Kehraus, S., Siering, C. and König, G.M. 2010. Hydroxylated sclerosporin derivatives from the marine derived fungus *Cadophora malorum*. *J. Nat. Prod.* **73**, 476-478. doi:10.1021/np900608d
57. Wu, B., Wu, X., Sun, M. and Li, M. 2013. Two novel tyrosinase inhibitory sesquiterpenes induced by $CuCl_2$ from a marine derived fungus *Pestalotiopsis* sp. Z233. *Mar. Drugs.* **11**, 2713-2721. doi:10.3390/md11082713
58. Gao, S.S., Li, X.M., Zhang, Y., Li, C.S. and Wang, B.G. 2011. Conidiogenones H and I, two new diterpenes of cyclopiane class from a marine derived endophytic fungus *Penicillium chrysogenum* QEN24S. *Chem. Biodivers.* **8**, 1748-1753. doi:10.1002/cbdv.201000378
59. Sun, H.F., Li, X.M., Meng, L., Cui, C.M., Gao, S.S., Li, C.S., Huang, C.G. and Wang, B.G. 2012. Asperolides A-C, tetranorlabdane diterpenoids from the marine alga derived endophytic fungus *Aspergillus wentii* EN48. *J. Nat. Prod.* **75**, 148-152. doi:10.1021/np2006742
60. Ishino, M., Kiyomichi, N., Takatori, K., Sugita, T., Shiro, M., Kinoshita, K., Takahashi, K. and Koyama, K. 2010. Phomactin I, 13-epi-Phomactin I, and Phomactin J, three novel diterpenes from a marine derived fungus. *Tetrahedron.* **66**, 2594-2597. doi:10.1016/j.tet.2010.02.040
61. Huang, Y.F., Li, L.H., Tian, L., Qiao, L., Hua, H.M. and Pei, Y.H. 2006. Sg1714, a novel isocoumarin from a marine fungus *Alternaria tenuis* Sg171. *J. Antibiot.* **59**, 355-357. doi:10.1038/ja.2006.50
62. Li, X., Li, X.M., Xu, G.M., Li, C.S. and Wang, B.G. 2014. Antioxidant metabolites from marine alga derived fungus *Aspergillus wentii* EN48. *Phytochem. Lett.* **7**, 120-123. doi:10.1016/j.phytol.2013.11.008
63. Fang, W., Lin, X., Wang, J., Liu, Y., Tao, H. and Zhou, X. 2016. Asperpyrone-type bis-naphtho-γ-pyrones with COX-2–inhibitory activities from marine-derived fungus *Aspergillus niger*. *Molecules.* **21**, 941.
64. Liu, X.H., Tang, X.Z., Miao, F.P. and Ji, N.Y. 2011. A new pyrrolidine derivative and steroids from an algicolous *Gibberella zeae* strain. *Nat. Prod. Commun.* **6**, 1243-1246.
65. Cui, C.M., Li, X.M., Li, C.S., Sun, H.F., Gao, S.S. and Wang, B.G. 2009. Benzodiazepine alkaloids from marine derived endophytic fungus *Aspergillus ochraceus*. *HCA.* **92**, 1366-1370. doi:10.1002/hlca.200900084
66. Zhang, L., Long, Y., Lei, X., Xu, J., Huang, Z., She, Z., Lin, Y., Li, J. and Liu, L. 2016. Azaphilones isolated from an alga-derived fungus *Penicillium* sp. ZJ-27. *Phytochem. Lett.* **18**, 180-186. doi:10.1016/j.phytol.2016.10.010
67. Tsuda, M., Kasai, Y., Komatsu, K., Sone, T., Tanaka, M., Mikami, Y. and Kobayashi, J. 'ichi. 2004. Citrinadin A, a novel pentacyclic alkaloid from marine derived fungus *Penicillium citrinum*. *Org. Lett.* **6**, 3087-3089. doi:10.1021/ol048900y
68. Mugishima, T., Tsuda, M., Kasai, Y., Ishiyama, H., Fukushi, E., Kawabata, J., Watanabe, M., Akao, K. and Kobayashi, J. 'ichi. 2005. Absolute stereochemistry of citrinadins A and B from marine derived fungus. *J. Org. Chem.* **70**, 9430-9435. doi:10.1021/jo051499o
69. Lin, A.Q., Du, L., Fang, Y.C., Wang, F.Z., Zhu, T.J., Gu, Q.Q. and Zhu, W.M. 2009. Iso-α-cyclopiazonic acid, a new natural product isolated from the marine derived fungus *Aspergillus flavus* CF3. *Chem. Nat. Compd.* **45**, 677. doi:10.1007/s1060000994338
70. Izumikawa, M., Hashimoto, J., Takagi, M. and Shinya, K. 2010. Isolation of two new terpeptin analogs JBIR81 and JBIR82 from a seaweed derived fungus, *Aspergillus* sp. SpD081030G1f1. *J. Antibiot.* **63**, 389-391. doi:10.1038/ja.2010.57
71. Cui, C.M., Li, X.M., Li, C.S., Proksch, P. and Wang, B.G. 2010a. Cytoglobosins A-G, cytochalasans from a marine derived endophytic fungus, *Chaetomium globosum* QEN14. *J. Nat. Prod.* **73**, 729-733. doi:10.1021/np900569t
72. Elsebai, M.F., Nazir, M., Kehraus, S., Egereva, E., Ioset, K.N., Marcourt, L., Jeannerat, D., Gütschow, M., Wolfender, J.L. and König, G.M. 2012. Polyketide skeletons from the marine alga derived fungus *Coniothyrium cereale*. *Eur. J. Org. Chem.* **2012**, 6197-6203. doi:10.1002/ejoc.201200700
73. König, G.M. and Wright, A.D. 1996. Marine natural products research: current directions and future potential. *Planta Med.* **62**, 193-211. doi:10.1055/s-2006-957861
74. Yanagihara, M., SasakiTakahashi, N., Sugahara, T., Yamamoto, S., Shinomi, M., Yamashita, I., Hayashida, M., Yamanoha, B., Numata, A., Yamori, T. and Andoh, T. 2005. Leptosins isolated from marine fungus *Leptoshaeria* species inhibit DNA topoisomerases I and/or II and induce apoptosis by inactivation of Akt/protein kinase B. *Cancer Sci.* **96**, 816-824. doi:10.1111/j.13497006.2005.00117.x

75. Cueto, M., Jensen, P.R. and Fenical, W. 2000. N-methylsansalvamide, a cytotoxic cyclic depsipeptide from a marine fungus of the genus *fusarium*. *Phytochemistry*. **55**, 223-226.
76. Li, Y., Li, X., Kim, S.K., Kang, J.S., Choi, H.D., Rho, J.R. and Son, B.W. 2004. Golmaenone, a new diketopiperazine alkaloid from the marine derived fungus *Aspergillus* sp. *Chem. Pharm. Bull*. **52**, 375-376.
77. Komatsu, K., Shigemori, H. and Kobayashi, J. 2001. Dictyonamides A and B, new peptides from marine derived fungus. *J. Org. Chem*. **66**, 6189-6192.
78. Elsebai, M.F., Kehraus, S. and König, G.M. 2013. Caught between triterpene and steroid metabolism: 4α-carboxylic pregnane derivative from the marine alga derived fungus *Phaeosphaeria spartinae*. *Steroids*. **78**, 880-883. doi:10.1016/j.steroids.2013.05.003
79. Cui, C.M., Li, X.M., Meng, L., Li, C.S., Huang, C.G. and Wang, B.G. 2010b. 7-norergosterolide, a pentalactone containing norsteroid and related steroids from the marine derived endophytic *Aspergillus ochraceus* EN31. *J. Nat. Prod*. **73**, 1780-1784. doi:10.1021/np100386q
80. Yang, R., Li, C., Lin, Y., Peng, G., She, Z. and Zhou, S. 2006. Lactones from a brown alga endophytic fungus (no. ZZF36) from the South China Sea and their antimicrobial activities. *Bioorganic Med. Chem. Lett.* **16**, 4205-4208. doi:10.1016/j.bmcl.2006.05.081
81. Li, Y., Li, X., Lee, U., Kang, J.S., Choi, H.D. and Sona, B.W. 2006. A new radical scavenging anthracene glycoside, asperflavin ribofuranoside, and polyketides from a marine isolate of the fungus *Microsporum*. *Chem. Pharm. Bull*. **54**, 882-883. doi:10.1248/cpb.54.882
82. Pontius, A., Krick, A., Kehraus, S., Brun, R. and König, G.M. 2008. Antiprotozoal activities of heterocyclic substituted xanthones from the marine derived fungus *Chaetomium* sp. *J. Nat. Prod*. **71**, 1579-1584. doi:10.1021/np800294q
83. Zhang, Y., Li, X.M. and Wang, B.G. 2012. Anthraquinone derivatives produced by marine derived fungus *Aspergillus versicolor* EN7. *Biosci. Biotechnol. Biochem.* **76,** 1774-1776. doi:10.1271/bbb.120047
84. Hawas, U.W., El-Beih, A.A. and El-Halawany, A.M. 2012. Bioactive anthraquinones from endophytic fungus *Aspergillus versicolor* isolated from red sea algae. *Arch. Pharm. Res.* **35**, 1749-1756. doi:10.1007/s122720121006x
85. Tarman, K., Palm, G.J., Porzel, A., Merzweiler, K., Arnold, N., Wessjohann, L.A., Unterseher, M. and Lindequist, U. 2012. Helicascolide C, a new lactone from an Indonesian marine algicolous strain of *Daldinia eschscholzii* (Xylariaceae, Ascomycota). *Phytochem. Lett.* **5**, 83-86. doi:10.1016/j.phytol.2011.10.006
86. Sun, R.R., Miao, F.P., Zhang, J., Wang, G., Yin, X.L. and Ji, N.Y. 2013. Three new xanthone derivatives from an algicolous isolate of *Aspergillus wentii*. *Magn. Reson. Chem*. **51**, 65-68. doi:10.1002/mrc.3903
87. Dai, J., Krohn, K., Flörke, U., Pescitelli, G., Kerti, G. and Papp T. 2010. Curvularin-type metabolites from the fungus *Curvularia* sp. isolated from a marine algae. *Eur. J. Org. Chem.* 6928-6937.
88. Zhang, Y., Li, X.M., Wang, C.Y. and Wang, B.G. 2007a. A new naphthoquinoneimine derivative from the marine algal-derived endophytic fungus *Aspergillus niger* EN-13. *Chin. Chem. Lett*. **18**, 951-953.
89. Li, H.-L., Li, X.-M., Liu, H., Meng, L.-H. and Wang, B.-G. 2016. Two new diphenylketones and a new xanthone from *Talaromyces islandicus* EN-501, an endophytic fungus derived from the marine red alga *Laurencia okamurai*. *Mar. Drugs.* **14**, 223. doi:10.3390/md14120223
90. Osterhage, C., König, G.M., Höller, U. and Wright, A.D. 2002. Rare sesquiterpenes from the algicolous fungus *Drechslera dematioidea*. *J. Nat. Prod*. **65**, 306-313.
91. Krohn, K., Dai, J., Flörke, U., Aust, H.J., Dräger, S. and Schulz, B. 2005. Botryane metabolites from the fungus *Geniculosporium* sp. isolated from the marine red alga *Polysiphonia*. *J. Nat. Prod*. **68**, 400-405. doi:10.1021/np0498206
92. Liu, X.H., Miao, F.P., Li, X.D., Yin, X.L. and Ji, N.Y. 2012a. A new sesquiterpene from an endophytic *Aspergillus versicolor* strain. *Nat. Prod. Commun*. **7**, 819-820.
93. Liu, X.H., Miao, F.P., Qiao, M.F., Cichewicz, R.H. and Ji, N.Y. 2012b. Terretonin, ophiobolin, and drimane terpenes with absolute configurations from an algicolous *Aspergillus ustus*. *RSC Adv*. **3**, 588-595. doi:10.1039/C2RA22701K
94. Qiao, M.F., Ji, N.Y., Liu, X.H., Li, K., Zhu, Q.M. and Xue, Q.Z. 2010. Indoloditerpenes from an algicolous isolate of *Aspergillus oryzae*. *Bioorg. Med. Chem. Lett.* **20**, 5677-5680. doi:10.1016/j.bmcl.2010.08.024
95. Gao, S.S., Li, X.M., Zhang, Y., Li, C.S. and Wang, B.G. 2011a. Conidiogenones H and I, two new diterpenes of cyclopiane class from a marine-derived endophytic fungus *Penicillium chrysogenum* QEN-24S. *Chem. Biodivers*. **8**, 1748-1753.
96. Gao, S.S., Li, X.M., Du, F.Y., Li, C.S., Proksch, P. and Wang, B.G. 2011b. Secondary metabolites from a marine-derived endophytic fungus *Penicillium chrysogenum* QEN-24S. *Mar. Drugs.* **9**: 59-70.
97. Sun, H., Li, X., Meng, L., Cui, C., Gao, S., Li, C., Huang, C. and Wang, B. 2012. Asperolides A-C, tetranorlabdane diterpenoids from the marine alga-derived endophytic fungus *Aspergillus wentii* EN-48. *J. Nat. Prod*. **75**, 148-152.
98. Liu, H., Li, X.-M., Liu, Y., Zhang, P., Wang, J.-N. and Wang, B.-G. 2016. Chermesins A–D: meroterpenoids with a drimane-type spirosesquiterpene skeleton from the marine algal-derived endophytic fungus *Penicillium chermesinum* EN-480. *J. Nat. Prod*. **79**, 806-811. doi:10.1021/acs.jnatprod.5b00893
99. Liang, X.-R., Miao, F.-P., Song, Y.-P., Guo, Z.-Y. and Ji, N.-Y. 2016. Trichocitrin, a new fusicoccane diterpene from the marine brown alga-endophytic fungus *Trichoderma citrinoviride* cf-27. *Nat. Prod. Res.* **30**, 1605-1610. doi:10.1080/14786419.2015.1126264

100. Yang, G., Sandjo, L., Yun, K., Leutou, A.S., Kim, G.D., Choi, H.D., Kang, J.S., Hong, J. and Son, B.W. 2011. Flavusides A and B, antibacterial cerebrosides from the marine derived fungus *Aspergillus flavus*. *Chem. Pharm. Bull*. **59**, 1174-1177.

101. Li, X., Li, X.M., Zhang, P. and Wang, B.G. 2015. A new phenolic enamide and a new meroterpenoid from marine alga derived endophytic fungus *Penicillium oxalicum* EN290. *J. Asian Nat. Prod. Res.* **17**, 1204-1212. doi:10.1080/10286020.2015.1117454

102. Silva, E.D.De, Geiermann, A., Mitova, M.I., Kuegler, P., Blunt, J.W. and Cole, A.L.J. 2009. Isolation of 2-pyridone alkaloids from a New Zealand marine-derived *Penicillium* species. *J. Nat. Prod*. **72**: 477-479.

103. Miao, F., Li, X., Liu, X., Cichewicz, R.H. and Ji, N. 2012. Secondary metabolites from an algicolous *Aspergillus versicolor*strain. *Mar. Drugs.* **10**, 131-139.

104. Zhang, Y., Li, X.M. and Wang, B.G. 2007C. Nigerasperones A-C, new monomeric and dimeric naphtho-g-pyrones from a marine alga-derived endophytic fungus *Aspergillus niger* EN-13. J. Antibiot. **60**: 204-210.

105. Osterhage, C., Kaminsky, R., König, G.M. and Wright, A.D. 2000. Ascosalipyrrolidinone A, an antimicrobial alkaloid, from the obligate marine fungus *Ascochyta salicorniae*. *J. Org. Chem*. **65**, 6412-6417. doi:10.1021/jo000307g

106. Zhuravleva, O.I., Afiyatullov, S.S., Denisenko, V.A., Ermakova, S.P., Slinkina, N.N., Dmitrenok, P.S. and Kim, N.Y. 2012. Secondary metabolites from a marine derived fungus *Aspergillus carneus* Blochwitz. *Phytochemistry*. **80**, 123-131. doi:10.1016/j.phytochem.2012.05.008

107. Zhang, P., Mándi, A., Li, X.M., Du, F.Y., Wang, J.N., Li, X., Kurtán, T. and Wang, B.G. 2014. Varioxepine A, a 3-H-oxepinecontaining alkaloid with a new oxacage from the marine algal derived endophytic fungus *Paecilomyces variotii*. *Org. Lett.* **16**, 4834-4837. doi:10.1021/ol502329k

108. Zhang, P., Li, X.M., Wang, J.N. and Wang, B.G. 2015b. Oxepine containing diketopiperazine alkaloids from the algal derived endophytic fungus *Paecilomyces variotii* EN291. *HCA.* **98**, 800-804. doi:10.1002/hlca.201400328

109. Du, F.Y., Li, X.M., Song, J.Y., Li, C.S. and Wang, B.G. 2014. Anthraquinone derivatives and an orsellinic acid ester from the marine alga derived endophytic fungus *Eurotium cristatum* EN220. *HCA.* **97**, 973-978. doi:10.1002/ hlca.201300358

110. Yang, H., fang, L.I. and Naiyun, J.I. 2016. Alkaloids from an algicolous strain of *Talaromyces* sp. *Chin. J. Oceanol. Limnol*. 1-5.

111. Du, F.-Y., Li, X., Li, X.-M., Zhu, L.-W. and Wang, B.-G. 2017. Indolediketopiperazine alkaloids from *Eurotium cristatum* EN-220, an endophytic fungus isolated from the marine alga *Sargassum thunbergii*. *Mar. Drugs.* **15**, 24. doi:10.3390/md15020024

112. Gao, S.S., Li, X.M., Li, C.S., Proksch, P. and Wang, B.G. 2011. Penicisteroids A and B, antifungal and cytotoxic polyoxygenated steroids from the marine alga derived endophytic fungus *Penicillium chrysogenum* QEN24S. *Bioorganic Med. Chem. Lett.* **21**, 2894-2897. doi:10.1016/j.bmcl.2011.03.076

113. Liu, X.F., Miao, F., Liang, X. and Ji, N. 2014. Ergosteroid derivatives from an algicolous strain of *Aspergillus ustus*. *Nat. Prod. Lett.* **28**, 1182-1186.

114. Sebastianes, F.L.S., Cabedo, N., Aouad, N.E., Valente, A.M.M.P., Lacava, P.T., Azevedo, J.L., Pizzirani-Kleiner, A.A. and Cortes, D. 2012. 3-hydroxypropionic acid as an antibacterial agent from endophytic fungi *Diaporthe phaseolorum. Curr. Microbiol.* **65**, 622-632. doi:10.1007/s0028401202064

115. Hawas, U.W., El-Halawany, A.M. and Ahmed, E.F. 2013. Hepatitis C virus NS3NS4A protease inhibitors from the endophytic *Penicillium chrysogenum* isolated from the red alga *Liagora viscida*. *Z. Naturforsch., C, J. Biosci.* **68**, 355-366.

116. Zhang, Y., Wang, S., Li, X.M., Cui, C.M., Feng, C. and Wang, B.G. 2007b. New sphingolipids with a previously unreported 9-methyl-C20-sphingosinemoiety from a marine algicolous endophytic fungus *Aspergillus niger* EN-13. *Lipids.* **42**, 759-764.

117. Puri, S. C., Nazir, A., Chawla, R., Arora, R., Riyaz-ul-Hasan, S., Amna, T., Ahmed, B., Verma, V., Singh, S., Sagar, R., Sharma, A., Kumar, R., Sharma, R.K., and Qazi, G. N. 2006. The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. *J. Biotechnol.* **122**, 494-510. doi:10.1016/j.jbiotec. 2005.10.015

118. Song, Y. C., Huang, W. Y., Sun, C., Wang, F. W., and Tan, R. X. 2005. Characterization of graphislactone A as the antioxidant and free radical-scavenging substance from the culture of *Cephalosporium* sp. IFB-E001, an endophytic fungus in *Trachelospermum jasminoides*. *Biol. Pharm. Bull.* **28**, 506-509. doi:10.1248/bpb.28.506

119. Lee, J. C., Lobkovsky, E., Pliam, N. B., Strobel, G., and Clardy, J. 1995. Subglutinols A and B: immunosuppressive compounds from the endophytic fungus *Fusarium subglutinans*. *J. Org. Chem.* **60**, 7076-7077.