Endophytes from marine macroalgae: promising sources of novel natural products

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Endophytic fungi are emerging as an excellent source of bioactive natural products. Though much of the research on endophytes and the natural products that they produce has focused on those isolated from terrestrial plants, endophytes of marine macroalgae have recently gained attention as an untapped source of biodiversity with the potential to yield novel bioactive metabolites. Recent work on the endophytic fungal assemblages of macroalgae has highlighted the scale of biodiversity and chemical diversity associated with fungal endophytes of macroalgae. The array of fungal species isolated and the discovery of new natural products exhibiting antimicrobial, anticancer and antiviral activities give a glimpse of the potential of macroalgal endophytes. The aim of this review is to highlight recent findings relating to endophytes of marine macroalgae with particular focus on the biodiversity of the endophytes associated with each macroalgal host, the geographical location of host alga and the biological activities exhibited by the natural products of these endophytic fungi.

Keywords: Bioactive metabolites, endophytic fungi, marine macroalgae, natural products.

Introduction

ENDOPHYTIC fungi are universally found in the plant kingdom[1–3]. The number of endophytes that can colonize a single plant ranges from just a few to hundreds[1] with each association assumed to be unique but characterized as somewhere between symbiotic and pathogenic[4].

While the relationship between plant host and endophyte is not always understood, many endophytes enhance host plant fitness through the production of bioactive compounds, improving survival against environmental stresses as well as promoting plant growth[1]. These functional metabolites are the target of current research in drug discovery[4–6].

With the knowledge that many terrestrial plants are associated with endophytes able to produce bioactive compounds, endophytes from marine plants and macroalgae are gaining special interest because of their existence in an ecosystem distinguished by resource limitations such as temperature, light availability, salinity and osmotic stress[4,7]. Indeed, endophytic fungi from various macroalgal hosts are increasingly being identified as sources of bioactive compounds with medicinal relevance (e.g. by exhibiting anticancer, antimicrobial and antifungal activities to name a few).

Despite this, our knowledge of the fundamental aspects of macroalgal endophyte biology is remarkably sparse and majority of the studies that have been performed on macroalgal endophytes provide little information that can meaningfully increase our understanding. This review will highlight the current state of knowledge relating to fungal endophytes of marine macroalgae with a particular focus on the geography and taxonomy of the algal hosts, the diversity and taxonomy of the fungal endophytes, and the reported bioactivity of extracts and natural products obtained from the fungi. Our aim is twofold: first to provide a comprehensive resource for researchers in the field and secondly, to highlight the deficiencies in the field to be addressed in future studies.

Geographic location of macroalgae

When evaluating the global distribution of algal endophytes, there exist discrepancies in the literature. While some studies are survey-based where researchers have attempted to maximize the number of hosts collected and diversity of endophytes[8–12], others are focused on the endophytes of a single macroalgal host or a single endophyte for the purpose of chemical elucidation and bioactivity assays[13–21]. Few studies have been performed screening marine macroalgae for their endophytic fungi. Most of the information on endophytic fungi in marine macroalgae comes from a study conducted by Suryanarayanan *et al.*[9] in India. As a result of this work, studies concerning the diversity of fungal endophytes and their potential for bioactive natural products have also been performed in Canada, Malaysia and the United Kingdom (UK)[10–12].

Nearly 100 marine macroalgae have been investigated for their endophytic fungi (Table 1), though approximately 75% of them have been investigated from just six locations (Baltic Sea, Canada, China, India, North Sea and

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Table 1. Summary of associated fungal endophytes classified by location

Location	Algal host	Fungal endophyte	Reference
Northern hemisphere			
Azores	*Valonia utricularis* (g)	*Chaetomium* sp.	32
Baltic Sea	*Enteromorpha* sp. (g)	*Coniothyrium cereale*	20, 21
		Wardomyces anomalus	14
	Fucus sp. (b)	*Dendryphiella arenaria*	23
		Phoma sp.	
	Polyides rotundus (r)	Unidentified	
	Polysiphonia sp. (r)	*Colletotrichum* sp.	
		Geniculosporium sp.	61
		Geniculosporium sp.	23
	Ulva linza (g)	*Alternaria* sp.	
Canada (Atlantic coast)	*Ascophyllum nodosum* (b)	*Aspergillus* sp. II	
		Mycosphaerella ascophylli	37, 38, 52, 53, 54, 55, 56, 87
	Chondrus crispus (r)	*Aspergillus* sp. I	11
		Penicillium crustosum I	
	Devaleraea ramentacea (r)	*Aureobasidium pullulans* I	
		Botrytis sp. I	
		Botrytis sp. II	
		Cladosporium sp.	
		Coniothyrium sp.	
		Penicillium decumbens I	
		Trametes versicolor	
		Septate pigmented I	
		Septate pigmented II	
		Septate pigmented III	
		Sterile hyaline I	
		Sterile hyaline II	
		White fluffy II	
	Fucus spiralis (b)	Black hyaline I	
		Pigmented hyaline I	
		Sterile hyaline XV	
		Septate pigmented V	
	Fucus vesiculosus (b)	Sterile hyaline XXI	
	Mastocarpus stellatus (r)	Coelomycete I	
		Penicillium decumbens II	
		Penicillium sp.	
		Red yeast I	
		Red yeast II	
		Sterile hyaline III	
		Sterile hyaline IV	
		Septate pigmented IV	
	Palmaria palmata (r)	*Botrytis* sp. III	
		Helicomyces sp.	
		Hypoxylon sp.	
		Penicillium chrysogenum I	
		Penicillium crustosum II	
		Penicillium decumbens III	
		Sterile hyaline V	
		Sterile hyaline VI	
		Sterile hyaline VII	
	Polysiphonia lanosa (r)	*Aureobasidium pullulans* II	
		Botryotinia fuckeliana	
		Sterile hyaline VIII	
		Sterile hyaline IX	
		Sterile hyaline X	
	Porphyra purpurea (r)	Sterile hyaline XI	
		Sterile hyaline XII	
	Porphyra umbilicalis (r)	*Aspergillus sydowii*	
		Sterile hyaline XIII	
		Sterile hyaline XIV	
	Saccharina latissima (b)	*Aspergillus* sp. III	

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
		Penicillium chrysogenum II	
		Penicillium chrysogenum III	
		Penicillium soppii I	
		Black hyaline II	
		Pigmented hyaline IV(Red)	
		Sterile beige I	
		Sterile beige II	
		Sterile hyaline XVI	
		White hyaline I	
		White hyaline II	
		White hyaline IV	
	Spongomorpha arcta (g)	*Penicillium soppii* II	
		Penicillium spinulosum	
		Penicillium sp.	
		Black hyaline III	
		Pigmented hyaline V	
		Pigmented hyaline VI	
		Pigmented hyaline VII	
		Sterile beige III	
		Sterile hyaline XVII	
		Sterile hyaline XVIII	
		White hyaline III	
	Ulva lactuca (g)	*Penicillium chrysogenum* IV	
		Septate pigmented VII	
		Sterile hyaline XX	
	Ulva intestinalis (g)	*Aspergillus* sp. V	
		Pigmented hyaline VIII	
		Septate pigmented VI	
		Septate pigmented VIII	
		Sterile hyaline XIX	
China	*Chondrus ocellatus* (r)	*Penicillium echinulatum*	64
	Codium fragile (g)	*Aspergillus versicolor*	66
		Gibberella zeae	65
		Trichoderma longibrachiatum	69
	Colpomenia sinuosa (b)	*Aspergillus niger*	16, 17, 18, 19, 89
	Corallina officinalis (r)	*Aspergillus flavus*	31
	Enteromorpha prolifera (g)	Unidentified fungus 9	8
		Unidentified fungus 10	
	Gelidium amansii (r)	Unidentified fungus 2	
	Gracilaria lemaneiformis (r)	Unidentified fungus 3	
		Unidentified fungus 4	
	Gracilariopsis sp. (r)	Unidentified	71
	Gymnogongrus flabelliformis (r)	*Aspergillus wentii*	81
	Heterosiphonia japonica (r)	*Aspergillus oryzae*	29, 30
	Laurencia similis (r)	*Exophialia oligosperma*	62
	Laurencia sp. (r)	*Alternaria alternata*	48
	Laurencia sp. (r)	*Penicillium chrysogenum*	49, 50, 51
	Polysiphonia urceolata (r)	*Chaetomium globosum*	86
	Rhodomela confervoides (r)	Unidentified fungus 1	8
	Sargassum fusiforme (b)	*Aspergillus wentii*	70
	Sargassum horneri (b)	*Pestalotiopsis* sp.	26
	Sargassum kjellmanianum (b)	*Aspergillus ochraceus*	28
	Sargassum palladium (b)	*Penicillium chrysogenum*	34
	Sargassum thunbergii (b)	*Aspergillus versicolor*	68
		Eurotium cristatum	39
		Unidentified fungus 5	8
		Unidentified fungus 6	
		Unidentified fungus 7	
		Penicillium glabrum	
	Sargassum sp. (b)	*Aspergillus wentii*	63
		Aspergillus wentii	80, 82

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
		Aspergillus wentii	90
		Unidentified fungus	88
	Ulva pertusa (g)	*Chaetomium globosum*	27, 35
		Unidentified fungus 11	8
		Unidentified fungus 12	
	Undaria pinnatifida (b)	*Guignardia* sp.	85
Egypt	*Ulva* sp. (g)	*Penicillium* sp.	47
France		*Dendryphiella salina*	
India	*Acanthophora spicifera* (r)	*Aspergillus sydowii*	84
	Caulerpa racemosa (g)	*Aspergillus niger*	9
		Aspergillus terreus	
		Aspergillus sp. 2	
		Aspergillus sp. 4	
		Aureobasidium pullulans	
		Chaetomium sp. 1	
		Cladosporium sp. 1	
		Fusarium sp. 2	
		Fusarium sp. 4	
		Fusarium sp. 5	
		Mucor sp.	
		Penicillium sp. 1	
		Phoma sp.	
		Pyrenocheta sp.	
		Sterile form 1	
		Yeast sp. 1	
	Caulerpa scalpelliformis (g)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Curvularia sp. 1	
		Paecilomyces sp. 1	
		Penicillium sp. 1	
	Caulerpa sertularioides (g)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Chaetomium sp. 1	
		Cladosporium sp. 1	
		Fusarium sp. 2	
		Myrothecium sp.	
		Penicillium sp. 1	
		Phialophora sp.	
		Sterile form 1	
		Yeast sp. 1	
	Dictyota dichotoma (b)	*Aspergillus niger*	
		Aspergillus terreus	
		Trichoderma sp.	
		Sterile form 1	
	Gelidiella acerosa (r)	*Alternaria* sp.	
		Aspergillus niger	
		Aspergillus terreus	
		Aspergillus versicolor	
		Nigrospora sp. 1	
		Penicillium sp. 1	
	Gelidiella acerosa (r)	*Phoma* sp.	
		Sterile form 1	
	Gracilaria crassa (r)	*Trichoderma* sp.	
		Sterile form 1	
	Gracilaria edulis (r)	*Aspergillus terreus*	
		Nigrospora sp. 1	
		Paecilomyces sp. 1	
	Gracilaria sp. (r)	*Aphanocladium* sp.	
		Aspergillus niger	
		Aspergillus terreus	

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
		Monilia sp.	
		Paecilomyces sp. 2	
		Yeast sp. 2	
	Grateloupia lithophila (r)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Chaetomium sp. 1	
		Cladosporium sp. 1	
		Emericella nidulans	
		Nigrospora sp. 1	
		Sterile form 1	
		Yeast sp. 1	
	Halimeda macroloba (g)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Aspergillus sp. 5	
		Paecilomyces sp. 1	
		Penicillium sp. 1	
		Trichoderma sp.	
		Yeast sp. 1	
	Halymenia sp. 1 (r)	*Aspergillus niger*	
		Aspergillus sp. 2	
		Aspergillus terreus	
		Chaetomium sp. 1	
		Cladosporium sp. 1	
		Coelomycete form 2	
		Emericella nidulans	
		Paecilomyces sp. 1	
		Phoma sp.	
	Halymenia sp. 2 (r)	*Aspergillus niger*	
		Aspergillus sp. 2	
		Aspergillus terreus	
		Cladosporium sp. 1	
		Drechslera sp. 1	
		Emericella nidulans	
		Penicillium sp. 1	
		Yeast sp. 1	
	Lobophora variegata var. *indica* (b)	*Aspergillus niger*	
		Aspergillus terreus	
		Chaetomium sp. 1	
		Emericella nidulans	
		Nigrospora sp. 1	
		Sterile form 3	
		UNI 1	
	Padina gymnospora (b)	*Aspergillus terreus*	
		Chaetomium sp. 1	
		Cladosporium sp. 1	
		Cladosporium sp. 2	
		Penicillium sp. 1	
		Phoma sp.	
		Trichoderma sp.	
		Sterile form 1	
		Sterile form 2	
	Padina tetrastromatica (b)	*Acremoniella* sp.	
		Ascotricha sp.	
		Aspergillus niger	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Aspergillus sp. 4	
		Aspergillus sp. 5	
		Chaetomium sp. 1	
		Monodictys sp.	

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
		Paecilomyces sp. 1	
		Penicillium sp. 1	
		Phialophora sp.	
		Sterile form 2	
	Portieria hornemanii (r)	*Aspergillus terreus*	
		Aspergillus sp. 2	
		Cladosporium sp. 1	
		Emericella nidulans	
		Memnoniella sp.	
		Penicillium sp. 1	
		Penicillium sp. 2	
		Phomopsis sp.	
		Trichophyton like	
		Trimmatostroma sp.	
		Sterile form 1	
		Yeast sp. 2	
		Yeast sp. 4	
	Sargassum ilicifolium (b)	*Aspergillus terreus*	
		Sterile form 1	
	Sargassum sp. (b)	*Alternaria* sp. 5	
		Aspergillus niger	
		Aspergillus terreus	
		Colletotrichum sp. 1	
		Curvularia lunata	
		Drechslera sp. 1	
		Helicosporium sp.	
		Nigrospora sp. 1	
		Oidiodendron sp.	
		Penicillium sp. 1	
		Taeniolella sp.	
		Varicosporium sp.	
		Sterile form 1	
		Sterile form 2	
		Sterile form 4	
		Sterile form 12	
		Yeast sp. 1	
	Sargassum wightii (b)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Aspergillus sp. 10	
		Aspergillus sp. 11	
		Cladosporium sp. 1	
		Coelomycete form 2	
		Nigrospora sp. 1	
		Paecilomyces sp. 1	
		Penicillium sp. 1	
		Sterile form 1	
		Sterile form 2	
		Yeast sp. 1	
		Yeast sp. 3	
	Stoechospermum marginatum (b)	*Alternaria* sp. 1	
		Aspergillus terreus	
		Chaetomium sp. 1	
		Emericella nidulans	
		Nigrospora sp. 1	
		Sterile form 3	
	Turbinaria decurrens (b)	*Alternaria* sp. 1	
		Aspergillus terreus	
		Chaetomium sp. 1	
		Chaetomium sp. 2	
		Chaetomium sp. 3	
		Curvularia sp. 1	

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
		Drechslera sp. 1	
		Emericella nidulans	
		Nigrospora sp. 1	
		Phialophora sp.	
		Pseudogymnoascus-like	
		Sterile form 1	
		UNI 2	
	Turbinaria sp. (b)	*Alternaria* sp. 3	
		Alternaria sp. 4	
		Alternaria sp. 5	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Aspergillus sp. 4	
		Aspergillus sp. 12	
		Chaetomium sp. 3	
		Cladosporium sp. 1	
		Cladosporium sp. 3	
		Colletotrichum sp. 1	
		Curvularia lunata	
		Curvularia tuberculata	
		Curvularia sp. 3	
		Drechslera papendorfii	
		Drechslera sp. 1	
		Emericella nidulans	
		Fusarium sp. 5	
		Monodictys sp.	
		Paecilomyces sp. 1	
		Phaeotrichoconis sp.	
		Sterile form 1	
		UNI 3	
		Varicosporium sp.	
		Yeast sp. 1	
	Turbinaria conoides (b)	*Aspergillus terreus*	
		Aspergillus sp. 5	
		Chaetomium sp. 1	
		Chaetomium sp. 2	
		Cladosporium sp. 1	
		Emericella nidulans	
		Phoma sp.	
		Sterile form 2	
		Sterile form 3	
	Ulva fasciata (g)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Chaetomium sp. 1	
		Curvularia lunata	
		Curvularia sp. *3*	
		Paecilomyces sp. 1	
		Sterile form 3	
		Yeast sp. 1	
		Yeast sp. 6	
	Ulva lactuca (g)	*Aspergillus niger*	
		Aspergillus terreus	
		Aspergillus sp. 2	
		Chaetomium sp. 1	
		Cladosporium sp. 1	
		Nigrospora sp. 1	
		Penicillium sp. 1	
Malaysia	*Caulerpa lentillifera* (g)	Unidentified fungus 3	10
		Unidentified fungus 4	
		Unidentified fungus 5	

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
		Unidentified fungus 6	
	Caulerpa racemosa (g)	Unidentified fungus 7	
		Unidentified fungus 8	
	Caulerpa racemosa variant (g)	Unidentified fungus 11	
	Padina australis (b)	Unidentified fungus 9	
		Unidentified fungus 10	
	Sargassum oligocystum (b)	Unidentified fungus 12	
		Unidentified fungus 13	
		Unidentified fungus 14	
		Unidentified fungus 15	
	Turbinaria conoides (b)	Unidentified fungus 1	
		Unidentified fungus 2	
Mediterranean Sea	*Cladostephus spongius* (b)	*Acremonium* sp.	15
	Plocamium sp. (r)	*Nodulisporium* sp.	75
	Unidentified green alga	*Monodictys putredinis*	25
	Unidentified	*Chaetomium* sp.	77
		Emericella nidulans var. *acristata*	60
	Unidentified	*Nodulisporium* sp.	76
North Sea	*Ceramium* sp. (r)	*Phaeospaeria spartinae*	41, 42
	Fucus vesiculosus (b)	*Penicillium* sp.	23
		Phoma sp.	
		Tolypocladium inflatum	
	Fucus sp. (b)	*Arthrinium* sp.	
	Laminaria digita (b)	*Dendryphiella salina*	
	Plocamium sp. (r)	*Acremonium* sp.	75
	Polysiphonia violacea (r)	*Apiospora montagnei*	58
	Ulva sp. (g)	*Ascochyta salicorniae*	72
		Ascochyta salicorniae	78
Sri Lanka	*Laurencia ceylanica* (r)	*Aspergillus terreus*	57
United Kingdom (Isle of Wight)	*Ascophyllum nodosum* (b)	*Mycosphaerella ascophylli*	79
	Chondrus crispus (r)	*Lautitia danica*	
	Dilsea carnosa (r)	*Mycaureola dilseae*	
United Kingdom (Lulworth Coast)	*Fucus vesiculosus* (b)	*Dendryphiella salina*	23
	Fucus sp. (b)	*Dendryphiella salina*	
United Kingdom (Shetland Islands)	*Ascophyllum nodosum* (b)	*Aspergillus fumigatus* I	12
		Cladosporium sp. I	
		Dendryphiella salina	
		Lichtheimia corymbifera	
	Fucus serratus (b)	*Aspergillus fumigatus* V	
		Aspergillus fumigatus VI	
		Coniothyrium sp. II	
		Coniothyrium sp. III	
		Penicillium sp. VII	
	Fucus spiralis (b)	*Penicillium* sp. V	12, 44
		Penicillium sp. VI	12
		Sterile beige VIII	
		Sterile beige IX	
		Sterile beige X	
		Sterile beige XI	
		Sterile pigmented VI	
	Fucus vesiculosus (b)	*Alternaria* sp.	
		Aspergillus fumigatus II	
		Aspergillus fumigatus III	
		Aspergillus fumigatus IV	
		Chalara sp.	
		Coniothyrium sp. I	
		Penicillium sp. I	
		Sterile beige I	
		Sterile beige II	

(*Contd*)

Table 1. (*Contd*)

Location	Algal host	Fungal endophyte	Reference
	Plocamium cartilagineum (r)	*Acremonium* sp.	
		Cladosporium sp. II	
		Metschnikowia sp.	
		Penicillium biourgeianum	
		Sterile beige VI	
		Sterile beige VII	
		Sterile pigmented IV	
		Sterile pigmented V	
	Polysiphonia lanosa (r)	*Phaeosphaeria* sp.	
		Sterile beige XII	
		Sterile beige XIII	
		Sterile beige XIV	
		Sterile beige XV	
		Sterile beige XVI	
		Sterile beige XVII	
		Sterile pigmented VII	
		Sterile pigmented VIII	
	Porphyra sp. (r)	*Microdochium* sp.	
		Rhodotorula mucilaginosa	
		Sterile beige III	
		Sterile beige IV	
		Sterile beige V	
	Ulva intestinalis (g)	*Bionectria ochroleuca*	
		Cordyceps sp.	
		Leptosphaeria sp.	
		Penicillium sp. III	
		Penicillium sp. IV	
		Penicillium sp. VIII	
		Pigmented filamentous	
		Septate hyaline I	
		Sterile pigmented II	
		Sterile pigmented III	
		Sterile pigmented IX	
	Ulva lactuca (g)	*Eurotium* sp.	
		Leotiomyceta sp.	
		Penicillium sp. II	
		Pseudeurotium bakeri	
		Stilbella fimetaria	
		Sterile pigmented I	
United States (California)	*Cystoseira* sp. (b)	*Haloguignardia irritans*	24
	Halidrys sp. (b)	*Haloguignardia irritans*	
United States (Florida)	*Ceramium* sp. (r)	*Chaetomium* sp.	23
	Digenea simplex (r)	*Dendryphiella arenaria*	
	Hypnea musciformis (r)	*Dendryphiella arenaria*	
	Sargassum sp. (b)	*Dendryphiella arenaria*	
		Corollospora sp.	
Southern hemisphere			
Brazil	*Bostrychia radicans* (r)	*Phomopsis longicolla*	43
Chile	*Prasiola crispa* (g)	*Mastodia tesselata*	74
Indonesia	*Gracilaria* sp. (r)	*Daldinia eschscholzii*	83
New Zealand	*Apophlaea* sp. (r)	*Mycosphaerella apophlaeae*	59
	Xiphophora gladiata (b)	*Penicillium* sp.	36
Unknown location	*Ascophyllum nodosum* (b)	*Mycosphaerella ascophylli*	45
		Mycosphaerella ascophylli	46
	Ceramium sp. (r)	*Phaeosphaeria spartinae*	40
	Fucus vesiculosus (b)	*Epicoccum* sp.	13
	Liagora viscida (r)	*Drechslera dematioidea*	73
	Unidentified	*Chaetomium* sp.	67

(r) denotes red algae belonging to the division Rhodophyta; (b) denotes brown algae belonging to the class Phaeophyceae and (g) denotes green algae belonging to the division Chlorophyta.

Table 2. Bioactivity of fungal endophytes isolated from marine macroalgal hosts

Bioactivity	Fungal endophyte	Algal host	Reference
AChE modulator	*Aspergillus flavus*	*Corallina officinalis* (r)	31
	Aspergillus oryzae	*Heterosiphonia japonica* (r)	29
Antialgal activity	*Aspergillus niger*	*Halimeda macroloba* (g)	
	Aspergillus niger	*Ulva lactuca* (g)	
	Aspergillus terreus	*Caulerpa scalpelliformis* (g)	
	Aspergillus terreus	*Caulerpa sertularioides* (g)	
	Aspergillus terreus	*Gracilaria edulis* (r)	
	Aspergillus terreus	*Halimeda macroloba* (g)	
	Aspergillus terreus	*Ulva lactuca* (g)	
	Aspergillus terreus	*Sargassum ilicifolium* (b)	
	Aspergillus sp. 2	*Halimeda macroloba* (g)	
	Aspergillus sp. 4	*Caulerpa racemosa* (g)	
	Aspergillus sp. 4	*Sargassum wightii* (b)	
	Chaetomium sp.	*Ulva lactuca* (g)	
	Chaetomium sp. 1	*Padina tetrastromatica* (b)	
	Chaetomium sp. 1	*Halymenia* sp. (r)	
	Fusarium sp.	*Sargassum wightii* (b)	
	Fusarium sp. 2	*Caulerpa sertularioides* (g)	
	Geniculosporium sp.	*Polysiphonia* sp. (r)	61
	Nigrospora sp.	*Ulva lactuca* (g)	9
	Nigrospora sp.	*Gracilaria edulis* (r)	
	Paecilomyces sp. 1	*Caulerpa scalpelliformis* (g)	
	Penicillium sp. 1	*Caulerpa scalpelliformis* (g)	
	Penicillium sp. 1	*Halimeda macroloba* (g)	
	Trichoderma sp.	*Halimeda macroloba* (g)	
	Trichoderma sp.	*Sargassum wightii* (b)	
	Sterile form 1	*Portieria hornemanii* (r)	
	Sterile form 2	*Sargassum wightii* (b)	
	Sterile form 3	*Lobophora variegate* (b)	
Anticancer activity	*Alternaria* sp.	*Ulva linz* (g)	23
	Apiospora montagnei	*Polysiphonia violacea* (r)	58
	Arthrinium sp.	*Fucus* sp. (b)	23
	Aspergillus niger	*Colpomenia sinuosa* (b)	89
	Aspergillus ochraceus	*Saargassum kjellmanianum* (b)	27
	Aspergillus versicolor	*Codium fragile* (g)	66
	Aspergillus wentii	*Sargassum fusiforme* (b)	70
	Chaetomium globosum	*Ulva pertusa* (g)	35
	Chaetomium sp.	*Ceramium* sp. (r)	23
	Colletotrichum sp.	*Polysiphonia* sp. (r)	
	Corollospora sp.	*Sargassum* sp. (b)	
	Emericella nidulans var. *acristata*	Unidentified	60
	Geniculosporium sp.	*Polysiphonia* sp. (r)	23
	Guignardia sp.	*Undaria pinnatifida* (b)	85
	Gibberella zeae	*Codium fragile* (g)	65
	Monodictys putredinis	Unidentified green alga	25
	Nodulisporium sp.	Unidentified	76
	Penicillium chrysogenum	*Sargassum palladium* (b)	34
	Penicillium chrysogenum	*Laurencia* sp. (r)	50
	Penicillium sp.	*Ulva* sp. (g)	47
	Penicillium sp.	*Fucus vesiculosis* (b)	23
	Phoma sp.	*Fucus* sp. (b)	
	Phoma sp.	*Fucus vesiculosis* (b)	
	Penicillium sp.	*Xiphophora gladiata* (b)	36
	Tolypocladium inflatum	*Fucus vesiculosis* (b)	23
	Unidentified fungus 1	*Turbinaria conoides* (b)	10
	Unidentified fungus 2	*Turbinaria conoides* (b)	
	Unidentified fungus 4	*Caulerpa lentillifera* (g)	
	Unidentified fungus 11	*Caulerpa racemosa* variant (g)	
	Unidentified fungus 12	*Sargassum oligocystum* (b)	
	Unidentified fungus 13	*Sargassum oligocystum* (b)	

(*Contd*)

Table 2. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Reference
	Unidentified fungus 14	*Sargassum oligocystum* (b)	
	Unidentified fungus 15	*Sargassum oligocystum* (b)	
Antimicrobial activity	*Alternaria* sp.	*Sargassum wighii* (b)	9
	Aspergillus fumigatus II	*Fucus vesiculosus* (b)	12
	Aspergillus fumigatus III	*Fucus vesiculosus* (b)	
	Aspergillus fumigatus IV	*Fucus vesiculosus* (b)	
	Aspergillus fumigatus V	*Fucus serratus* (b)	
	Aspergillus fumigatus VI	*Fucus serratus* (b)	12
	Aspergillus niger	*Colpomenia sinuosa* (b)	16, 17, 18, 19, 89
	Aspergillus niger	*Halimeda macroloba* (g)	9
	Aspergillus oryzae	*Heterospihonia japonica* (r)	30
	Aspergillus sydowii	*Porphyra umbilicalis* (r)	11
	Aspergillus terreus	*Caulerpa sertularioides* (g)	9
	Aspergillus terreus	*Caulerpa scalpelliformis* (g)	
	Aspergillus terreus	*Gracilaria edulis* (r)	
	Aspergillus terreus	*Ulva lactuca* (g)	
	Aspergillus terreus	*Halimeda macroloba* (g)	
	Aspergillus versicolor	*Codium fragile* (g)	66
	Aspergillus versicolor	*Sargassum thunbergii* (b)	68
	Aspergillus wentii	*Gymnogongrus flabelliformis* (r)	81
	Aspergillus wentii	*Sargassum* sp. (b)	80
	Aspergillus sp. 2	*Caulerpa scalpelliformis* (g)	9
	Aspergillus sp. 2	*Halimeda macroloba* (g)	
	Aspergillus sp. 4	*Sargassum wighii* (b)	
	Aspergillus sp. 10	*Sargassum wighii* (b)	
	Aspergillus sp. I	*Chondrus crispus* (r)	11
	Aspergillus sp. II	*Ascophyllum nodosum* (b)	
	Aspergillus sp. III	*Saccharina latissima* (b)	
	Aureobasidium pullulans I	*Devaleraea ramentacea* (r)	
	Aureobasidium pullulans II	*Polysiphonia lanosa* (r)	
	Botryotinia fuckeliana	*Polysiphonia lanosa* (r)	
	Botrytis sp. I	*Devaleraea ramentacea* (r)	
	Botrytis sp. II	*Devaleraea ramentacea* (r)	
	Botrytis sp. III	*Palmaria palmata* (r)	
	Chaetomium sp.	Unidentified	67
	Chaetomium sp. 1	*Halymenia* sp. (r)	9
	Chaetomium sp. 1	*Padina tetrastromatica* (b)	
	Cladosporium sp.	*Devaleraea ramentacea* (r)	11
	Cladosporium sp. 1	*Portieria hornemanii* (r)	9
	Cladosporium sp. 1	*Sargassum wighii* (b)	
	Cladosporium sp. 1	*Caulerpa racemosa* (g)	
	Cladosporium sp. II	*Plocamium cartilagineum* (r)	12
	Coniothyrium cereale	*Enteromorpha* sp. (g)	20
	Coniothyrium sp.	*Devaleraea ramentacea*	11
	Coniothyrium sp. I	*Fucus vesiculosus* (b)	
	Coniothyrium sp. II	*Fucus serratus* (b)	
	Coniothyrium sp. III	*Fucus serratus* (b)	
	Curvularia sp. 1	*Sargassum wighii* (b)	9
	Curvularia sp. 3	*Sargassum wighii* (b)	
	Daldinia eschscholzii	*Gracilaria* sp. (r)	83
	Emericella nidulans	*Sargassum wighii* (b)	9
	Emericella nidulans	*Halymenia* sp. (r)	
	Eurotium cristatum	*Sargassum thunbergii* (b)	39
	Eurotium sp.	*Ulva lactuca* (g)	12
	Fusarium sp.	*Sargassum wighii* (b)	9
	Fusarium sp. 2	*Caulerpa sertularioides* (g)	
	Guignardia sp.	*Undaria pinnatifida* (b)	85
	Helicomyces sp.	*Palmaria palmata* (r)	11
	Hypoxylon sp.	*Palmaria palmata* (r)	
	Leptosphaeria sp.	*Ulva intestinalis* (g)	12
	Microdochium sp.	*Porphyra* sp. (r)	

(*Contd*)

Table 2. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Reference
	Nigrospora sp.	*Gracilaria edulis* (r)	9
	Paecilomyces sp. 1	*Caulerpa scalpelliformis* (g)	
	Penicillium biourgeianum	*Plocamium cartilagineum* (r)	12
	Penicillium chrysogenum	*Laurencia* sp. (r)	49, 50, 51
	Penicillium chrysogenum I	*Palmaria palmata* (r)	11
	Penicillium chrysogenum II	*Saccharina latissima* (b)	
	Penicillium crustosum I	*Chondrus crispus* (r)	
	Penicillium crustosum II	*Palmaria palmata* (r)	
	Penicillium decumbens I	*Devaleraea ramentacea* (r)	
	Penicillium decumbens II	*Mastocarpus stellatus* (r)	
	Penicillium decumbens III	*Palmaria palmata* (r)	
	Penicillium echinulatum	*Chondrus ocellatus* (r)	64
	Penicillium glabrum	*Sargassum thunbergii* (b)	8
	Penicillium soppii II	*Spongomorpha arcta* (g)	11
	Penicillium spinulosum	*Spongomorpha arcta* (g)	
	Penicillium sp.	*Xiphophora gladiata* (b)	36
	Penicillium sp.	*Caulerpa scalpelliformis* (g)	9
	Penicillium sp. 1	*Portieria hornemanii* (r)	
	Penicillium sp. 1	*Caulerpa racemosa* (g)	
	Penicillium sp. 1	*Caulerpa sertularioides* (g)	
	Penicillium sp. 1	*Halimeda macroloba* (g)	
	Penicillium sp. I	*Fucus vesiculosus* (b)	12
	Penicillium sp. II	*Ulva lactuca* (g)	
	Penicillium sp. III	*Ulva intestinalis* (g)	
	Penicillium sp. IV	*Ulva intestinalis* (g)	
	Penicillium sp. V	*Fucus spiralis* (b)	12, 44
	Penicillium sp. VII	*Fucus serratus* (b)	12
	Penicillium sp. VIII	*Ulva intestinalis* (g)	
	Phaeosphaeria sp.	*Polysiphonia lanosa* (r)	
	Phomopsis sp.	*Portieria hornemanii* (r)	9
	Stilbella fimetaria	*Ulva lactuca* (g)	12
	Trametes versicolor	*Devaleraea ramentacea* (r)	11
	Trichoderma longibrachiatum	*Codium fragile* (g)	69
	Trichoderma sp.	*Sargassum wightii* (b)	9
	Black hyaline I	*Fucus spiralis* (b)	11
	Black hyaline II	*Saccharina latissima* (b)	
	Pigmented filamentous	*Ulva intestinalis* (g)	12
	Pigmented hyaline I	*Fucus spiralis* (b)	11
	Pigmented hyaline IV (Red)	*Saccharina latissima* (b)	
	Pigmented hyaline V	*Spongomorpha arcta* (g)	
	Pigmented hyaline VII	*Spongomorpha arcta* (g)	
	Red yeast I	*Mastocarpus stellatus* (r)	
	Sterile beige II	*Saccharina latissima* (b)	
	Sterile beige III	*Porphyra* sp. (r)	12
	Sterile beige IV	*Porphyra* sp. (r)	
	Sterile beige VII	*Plocamium cartilagineum* (r)	
	Sterile beige VIII	*Fucus spiralis* (b)	
	Sterile beige X	*Fucus spiralis* (b)	
	Sterile beige XI	*Fucus spiralis* (b)	
	Sterile beige XII	*Polysiphonia lanosa* (r)	
	Sterile beige XIII	*Polysiphonia lanosa* (r)	
	Septate hyaline I	*Ulva intestinalis* (g)	
	Septate pigmented I	*Devaleraea ramentacea* (r)	11
	Septate pigmented III	*Devaleraea ramentacea* (r)	
	Septate pigmented IV	*Mastocarpus stellatus* (r)	
	Septate pigmented V	*Fucus spiralis* (b)	
	Septate pigmented VI	*Ulva intestinalis* (g)	
	Septate pigmented VII	*Ulva lactuca* (g)	
	Septate pigmented VIII	*Spongomorpha arcta* (g)	
	Sterile hyaline I	*Devaleraea ramentacea* (r)	
	Sterile hyaline V	*Palmaria palmata* (r)	

(*Contd*)

Table 2. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Reference
	Sterile hyaline VI	*Palmaria palmata* (r)	
	Sterile hyaline VII	*Palmaria palmata* (r)	
	Sterile hyaline IX	*Polysiphonia lanosa* (r)	
	Sterile hyaline X	*Polysiphonia lanosa* (r)	
	Sterile hyaline XI	*Porphyra purpurea* (r)	
	Sterile hyaline XII	*Porphyra purpurea* (r)	
	Sterile hyaline XIII	*Porphyra umbilicalis* (r)	
	Sterile hyaline XIV	*Porphyra umbilicalis* (r)	
	Sterile hyaline XVII	*Spongomorpha arcta* (g)	
	Sterile hyaline XIX	*Ulva intestinalis* (g)	
	Sterile hyaline XX	*Ulva lactuca* (g)	
	Sterile pigmented I	*Ulva lactuca* (g)	12
	Sterile pigmented II	*Ulva intestinalis* (g)	
	Sterile pigmented V	*Plocamium cartilagineum* (r)	
	Sterile pigmented VI	*Fucus spiralis* (b)	
	Sterile pigmented VII	*Polysiphonia lanosa* (r)	
	Sterile pigmented VIII	*Polysiphonia lanosa* (r)	
	Sterile pigmented IX	*Ulva intestinalis* (g)	
	White fluffy II	*Devaleraea ramentacea* (r)	11
	White hyaline II	*Saccharina latissima* (b)	
	White hyaline III	*Spongomorpha arcta* (g)	
	White hyaline IV	*Saccharina latissima* (b)	
	Sterile form 1	*Portieria hornemanii* (r)	9
	Sterile form 1	*Caulerpa racemosa* (g)	
	Sterile form 2	*Sargassum wightii* (b)	
	Sterile form 3	*Turbinaria decurrens* (b)	
	Unidentified fungus	*Sargassum* sp. (b)	88
	Unidentified fungus 1	*Rhodomela confervoides* (r)	8
	Unidentified fungus 2	*Gelidium amansii* (r)	
	Unidentified fungus 3	*Gracilaria lemaneiformis* (r)	
	Unidentified fungus 4	*Gracilaria lemaneiformis* (r)	
	Unidentified fungus 5	*Sargassum thunbergii* (b)	
	Unidentified fungus 6	*Sargassum thunbergii* (b)	
	Unidentified fungus 9	*Enteromorpha prolifera* (g)	
	Unidentified fungus 10	*Enteromorpha prolifera* (g)	
	Unidentified fungus 11	*Ulva pertusa* (g)	
	Unidentified fungus 12	*Ulva pertusa* (g)	
Antioxidant activity	*Acremonium* sp.	*Cladostephus spongius* (b)	15
	Aspergillus niger	*Caulerpa scalpelliformis* (g)	9
	Aspergillus niger	*Colpomenia sinuosa* (b)	17
	Aspergillus ochraceus	*Sargassum kjellmanianum* (b)	28
	Aspergillus terreus	*Caulerpa scalpelliformis* (g)	9
	Aspergillus terreus	*Gracilaria edulis* (r)	
	Aspergillus terreus	*Sargassum ilicifolium* (b)	
	Aspergillus terreus	*Ulva lacuca* (g)	
	Aspergillus sp. 2	*Caulerpa scalpelliformis* (g)	
	Aspergillus wentii	*Sargassum* sp. (b)	63
	Chaetomium globosum	*Polysiphonia urceolata* (r)	86
	Curvularia sp. 1	*Caulerpa scalpelliformis* (g)	9
	Epicoccum sp.	*Fucus vesiculosus* (b)	13
	Fusarium sp. 4	*Caulerpa racemosa* (g)	9
	Guignardia sp.	*Undaria pinnatifida* (b)	85
	Paecilomyces sp. 1	*Caulerpa scalpelliformis* (g)	9
	Penicillium sp. 1	*Caulerpa scalpelliformis* (g)	
	Penicillium sp. 1	*Halimeda macroloba* (g)	
	Sterile form 1	*Caulerpa racemosa* (g)	
Antiplasmodial activity	*Ascochyta salicorniae*	*Ulva* sp. (g)	72
	Chaetomium sp.	Unidentified	77
	Drechslera dematioidea	*Liagora viscida* (r)	73
Inhibition of β-glucuronidase	*Aspergillus terreus*	*Laurencia ceylanica* (r)	57

(*Contd*)

Table 2. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Reference
Inhibtion of HLE	*Coniothyrium cereale*	*Enteromorpha* sp. (g)	21
	Phaeosphaeria spartinae	*Ceramium* sp. (r)	40, 41
Insecticidal activity	*Aspergillus niger*	*Caulerpa racemosa* (g)	9
	Aspergillus niger	*Ulva lactuca* (g)	
	Aspergillus terreus	*Caulerpa scalpelliformis* (g)	
	Aspergillus terreus	*Caulerpa sertularioides* (g)	
	Aspergillus terreus	*Gracilaria edulis* (r)	
	Aspergillus terreus	*Halimeda macroloba* (g)	
	Aspergillus terreus	*Sargassum ilicifolium* (b)	
	Aspergillus terreus	*Ulva lactuca* (g)	
	Aspergillus sp. 2	*Halimeda macroloba* (g)	
	Chaetomium sp. 1	*Ulva lactuca* (g)	
	Cladosporium sp. 1	*Caulerpa racemosa* (g)	
	Fusarium sp. 2	*Caulerpa sertularioides*(g)	
	Fusarium sp. 4	*Caulerpa racemosa* (g)	
	Paecilomyces sp. 1	*Caulerpa scalpelliformis* (g)	
	Penicillium sp. 1	*Caulerpa scalpelliformis* (g)	
	Penicillium sp. 1	*Halimeda macroloba* (g)	
	Sterile form 1	*Caulerpa racemosa* (g)	
Protein phosphatase inhibitor	*Ascochyta salicorniae*	*Ulva* sp. (g)	78
Tyrosine kinase inhibitor	*Chaetomium* sp.	*Valonia utricularis* (g)	32
	Drechslera dematioidea	*Liagora viscida* (r)	73
	Pestalotiopsis sp.	*Sargassum horneri* (b)	26
	Wardomyces anomalus	*Enteromorpha* sp. (g)	14

(r), (b) and (g), same as in Table 1.

UK). It should also be noted that red algae represent the greatest proportion of hosts investigated, with 41 species studied (Table 1). The number of hosts studied decreases substantially for the brown and green algae (32 and 19 respectively; Table 1). In the context of the conservative estimates by Guiry[22] (7000 red, 8000 green and 2000 brown algae worldwide), the 100 algal hosts investigated to date represent <1% of the available sources of endophytes. This suggests that much work remains to be done on the distribution of algal endophytes and their role as a promising source of chemical diversity.

It should be noted that several species have been studied in multiple locations (Table 1). Two studies performed by Flewelling *et al.*[11,12] investigated *Ascophyllum nodosum*, *Fucus spiralis*, *Fucus vesiculosus*, *Polysiphonia lanosa*, *Ulva lactuca* and *Ulva intestinalis* from both the Bay of Fundy, Canada and the Shetland Islands, UK. *Sargassum* spp. have also been investigated in multiple locations, including China, India, USA and France (Table 1).

Fungal biodiversity

A screening of marine macroalgae from the southern Indian coast for their endophytic fungi by Suryanarayanan *et al.*[9] indicated that from a total sample size of 281 fungal isolates (representing 72 distinct species), green algae yielded the lowest diversity of endophytic fungal species, whereas brown algae yielded the highest diversity. This is in contrast to the findings of Flewelling *et al.*[12], where over one quarter of the distinct fungi isolated came from the green algae, *U. lactuca* and *U. intestinalis*. In order to continue analysing this trend, further work is required globally, through the isolation of a larger number of fungal isolates from a greater sampling of macroalgae, to identify if there are individual species differences within the groups of macroalgae (red, green, brown), or to see whether the global geographic, climatic or seasonal differences may account for differences in fungal diversity.

Of the green algae studied thus far, *Caulerpa* spp. and *Ulva* spp. have the most diverse endophytic fungal symbionts with the majority recorded by Suryanarayanan *et al.*[9] and Flewelling *et al.*[12] in India and Shetland Islands respectively (Table 1). Forty-one red algae have been found to host fungal endophytes (Table 1). Of the red algae studied to date, *Portieria hornemanii*, *Gelidiella acerosa*, *Gracilaria* spp. and *Halymenia* spp. have displayed the greatest diversity of fungal endophytes, with the majority found in India[9]. Thirty-two species of brown algae have been shown to host fungal endophytes (Table 1). *Fucus* spp., *Padina* spp., *Sargassum* spp. and *Turbinaria* spp. have displayed the greatest diversity of endophytic fungi. *Alternaria* spp., *Chaetomium* spp. and *Cladosporium* spp. appear to lack host specificity, having been isolated as fungal endophytes from numerous locations and hosts

Table 3. Summary of the number of compounds isolated from endophytic fungi of marine macroalgae

Bioactivity	Fungal endophyte	Algal host	Number of compounds identified	Reference
AChE modulator	*Aspergillus flavus*	*Corallina officinalis* (r)	(8*E*,12*Z*)-10,11-dihydroxyoctadeca-8,12-dienoic acid 3β, 4α-dihydroxy-26-methoxyergosta-7,24(28)-dien-6-one Episterol (22*E*,24*R*)-ergosta-7,22-dien-3β, 5α,6α-triol (22*E*,24*R*)-ergosta-5,22-dien-3β-ol (*22E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one	31
	Aspergillus oryzae	*Heterosiphonia japonica* (r)	Asporyergosterol (22*E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one (22*E*,24*R*)-3β-hydroxyergosta-5,8,22-trien-7-one (22*E*,24*R*)-ergost-7,22-dien-3β, 5α,6β-triol (22*E*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3β-ol	29
Antialgal	*Geniculosporium* sp.	*Polysiphonia* sp. (r)	7-Hydroxy-10-methoxydeacetyldihydrobotrydial 7-Hydroxy-10-oxodehydrodihydrobotrydial 7,10-Dihydroxydehydrodihydrobotrydial 7-Hydroxy-10-methoxydehydrodihydrobotrydial 7-Hydroxy-10-ethoxydehydrodihydrobotrydial 7-Hydroxy-10-dehydroxydehydrodihydrobotrydial 7-Hydroxydeacetylbotryenalol 7,10-Dihydroxydeacetyldihydrobotrydial-1(10)-ene 4,10-Didehydroxy-7-hydroxydeacetyldihydrobotrydial-1(10),5(9)-diene 7-Hydroxy-10-dehydroxydeacetyldihydrobotrydial-1(10),5(9)-diene 15α-Hydroxy-14-aldehyde probotryan-4(5)-ene L-696,474 Cytochalasin U RKS-1778 Cytochalasin H	61
Anticancer	*Apiospora montagnei*	*Polysiphonia violacea* (r)	Myrocin A Apiosporic acid 9-Hydroxyhexylitaconic acid (–)-Hexylitaconic acid (+)-Epiepoxydon	58
	Aspergillus niger	*Colpomenia sinuosa* (b)	Isopyrophen Aspergillusol Pyrophen Cyclo-(L-Trp-L-Ile) Cyclo-(L-Trp-L-Phe) Cyclo-(L-Trp-L-Tyr)	89
	Aspergillus ochraceus	*Sargassum kjellmanianum* (b)	7-Nor-ergosterolide 3β,11α-dihydroxyergosta-8,24(28)-dien-7-one 3β-hydroxyergosta-8,24(28)-dien-7-one	27
	Aspergillus wentii	*Sargassum fusiforme* (b)	Aspewentin A Aspewentin B Aspewentin C	70
	Aspergillus wentii	*Sargassum* sp. (b)	Wentilactone B	90
	Chaetomium globosum	*Ulva pertusa* (g)	Cytoglobosin A Cytoglobosin B Cytoglobosin C Cytoglobosin D Cytoglobosin E Cytoglobosin F Cytoglobosin G Isochaetoglobosin D Chaetoglobosin F_{ex}	35
	Emericalla nidulans var. *acristata*	Unknown green alga	Arugosin G Arugosin H Arugosin A Arugosin B	60

(*Contd*)

Table 3. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Number of compounds identified	Reference
			Shamixanthone Emericellin Emindole DA Microperfuranone Sterigmatocystin	
	Gibberella zeae	*Codium fragile* (g)	3-Hydroxy-5-(hydroxymethyl)-4-(4′-hydroxyphenoxy) pyrrolidin-2-one (22*E*,24*R*)-7β,8β-epoxy-3β,5α,9α-trihydroxyergosta-22-en-6-one (22*E*,24*R*)-3β,5α,9α-trihydroxyergosta-7,22-dien-6-one (22*E*,24*R*)-3β,5α-dihydroxyergosta-7,22-dien-6-one (22*E*,24*R*)-ergosta-7,22-dien-3β,5α,6β-triol (22*E*,24*R*)-ergosta-5,22-dien-3β-ol (22*E*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3β-ol (22*E*,24*R*)-5α, 8α-epidioxyergosta-6,9(11),22-trien-3β-ol (22*E*,24*R*)-1(10 → 6)-*abeo*-ergosta-5,7,9,22-tetraen-3α-ol	65
	Monodictys putredinis	Unknown green alga	Monodictysin A Monodictysin B Monodictysin C Monodictyxanthone Monodictyphenone	25
	Nodulisporium sp.	Unknown	Noduliprevenone	76
	Penicillium chrysogenum	*Sargassum palladium* (b)	Chrysotriazole A Chrysotriazole B 2-(4-Hydroxybenzoyl)-4(3*H*)-quinazolinone 2-(4-Hydroxybenzyl)quinazolin-4(3*H*)-one *N*-[2-(4-Hydroxyphenyl)acetyl]formamide 2-(4-Hydroxyphenyl)acetylamide *N*-[(2*E*)-(4-Hydroxyphenyl)ethenyl]formamide *N*-[(2*Z*)-(4-Hydroxyphenyl)ethenyl]formamide	34
	Penicillium sp.	*Ulva* sp. (g)	Chromanone A	47
Anticancer; antimicrobial	*Aspergillus versicolor*	*Codium fragile* (g)	Albican-11,14-diol Sterigmatocystin 3-Hydroxy-5-(hydroxymethyl)-4-(4′-hydroxyphenoxy) pyrrolidin-2-one (1*H*-Indol-3-yl) oxoacetamide Indole-3-carboxylic acid Indole-3-acetic acid Indole-3-carboxaldehyde Volemolide	66
	Penicillium chrysogenum	*Laurencia* sp. (r)	Penicisteroid A Penicisteroid B Anicequol (22*E*,24*R*)-ergosta-4,6,8(14),22-tetraen-3-one (22*E*,24*R*)-ergosta-7,22-dien-3,6-dione (22*E*,24*R*)-5α,8α-epidioxyergosta-6,22-dien-3β-ol (22*E*,24*R*)-ergosta-5α,6α-epoxide-8, 22-dien-3β,7α-diol (22*E*,24*R*)-ergosta-7,22-dien-3β,5 α,6β-triol (22*E*,24*R*)-ergosta-7,22-dien-3β,6β-diol	50
	Penicillium sp.	*Xiphophora gladiata* (b)	PF1140 Deoxy-PF1140 Deoxyakanthomycin	36
	Guignardia sp.	*Undaria pinnatifida* (b)	Ergosterol peroxide Ergosterol Cyclo-(Tyr-Leu) Cyclo-(Phe-Phe) Cyclo-(Val-Leu) Cyclo-(Phe-Pro) Cyclo-(Leu-Ile)	85

(*Contd*)

Table 3. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Number of compounds identified	Reference
Antimicrobial	*Aspergillus niger*	*Colpomenia sinuosa* (b)	Asperamide A Asperamide B	19
			5,7-Dihydroxy-2-[1-(4-methoxy-6-oxo-6*H*-pyran-2-yl)-2-phenylethylamino]-[1,4] naphthoquinone	18
	Aspergillus oryzae	*Heterosiphonia japonica* (r)	Asporyzin A Asporyzin B Asporyzin C JBIR-03 Emindole SB Emeniveol	30
	Aspergillus versicolor	*Sargassum thunbergii* (b)	Asperversin A 9ξ-*O*-2(2,3-dimethylbut-3-enyl)brevianamide Q Brevianamide K Brevianamide M Aversin 6,8-di-*O*-methylnidurufin 6,8-di-*O*-methylaverufin 6-*O*-methylaverufin 5α,8α-Epidioxyergosta-6,22-dien-3β-ol Ergosta-7,22-diene-3β,5α,6β-triol	68
	Aspergillus versicolor	*Sargassum thunbergii* (b)	6β-methoxyergosta-7,22-diene-3β,5α-diol	68
	Aspergillus wentii	*Gymnogongrus flabelliformis* (r)	Yicathin A Yicathin B Yicathin C Alatinone 1,5-Dihydroxy-3-methoxy-7-methylanthraquinone 5-Hydroxy-1,3-dimethoxy-7-methylanthraquinone	81
	Aspergillus wentii	*Sargassum* sp. (b)	Asperolide A Asperolide B Asperolide C Tetranorditerpenoid derivative Wentilactone A Wentilactone B Botryosphaerin B LL-Z1271-β	80
	Chaetomium sp.	Unknown	Chaetocyclinone A Chaetocyclinone B Chaetocyclinone C	67
	Coniothyrium cereale	*Enteromorpha* sp. (g)	Coniosclerodin (*Z*)-Coniosclerodinol (*E*)-Coniosclerodinol (15*S*,17*S*)-(–)-Sclerodinol Coniosclerodinol Coniosclerodione Coniolactone (–)-7,8-Dihydro-3,6-dihydroxy-1,7,7,8-tetramethyl-5*H*-furo-[2′,3′ : 5,6]naphtho[1,8-bc]furan-5-one (–)-Sclerodin A	20
			Lamellicolic anhydride (–) Scleroderolide (–) Sclerodione	20
	Daldinia eschscholzii	*Gracilaria* sp. (r)	Helicascolide C Helicascolide A	83
	Eurotium cristatum	*Sargassum thunbergii* (b)	Cristatumin A Cristatumin B Cristatumin C Cristatumin D Neoechinulin A Isoechinulin A Variecolorin G	39

(*Contd*)

Table 3. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Number of compounds identified	Reference
			Preechinulin Tardioxopiperazine A Echinulin	
	Penicillium chrysogenum	*Laurencia* sp. (r)	Penicitide A Penicitide B 2-(2,4-Dihydroxy-6-methylbenzoyl)-glycerol 1-(2,4-Dihydroxy-6-methylbenzoyl)-glycerol Penicimonoterpene	49
	Penicillium chrysogenum	*Laurencia* sp. (r)	Conidiogenone H Conidiogenone I Conidiogenone B Conidiogenone C Conidiogenone D Conidiogenone F Conidiogenol	51
	Penicillium echinulatum	*Chondrus ocellatus* (r)	Arisugacin K Arisugacin J Arisugacin G Arisugacin C Territrem C	64
	Penicillium sp.	*Fucus spiralis* (b)	Cladosporin Epiepoformin Phyllostine Patulin	44
	Phomopsis longicolla	*Bostrychia radicans* (r)	18-deoxycytochalasin H Mycophenolic acid Dicerandrol C	43
	Trichoderma longibrachiatum	*Codium fragile* (g)	Harziandione	69
	Unidentified fungus	*Sargassum* sp. (b)	6-Oxo-de-*O*-methyllasiodiplodin (*E*)-9-Etheno-lasiodiplodin Lasiodiplodin de-*O*-Methyllasiodiplodin 5-Hydroxy-de-*O*-methyllasiodiplodin	88
Antimicrobial; Antioxidant	*Aspergillus niger*	*Colpomenia sinuosa* (b)	Nigerasperone A Nigerasperone B Nigerasperone C	17
Antioxidant	*Acremonium* sp.	*Cladostephus spongius* (b)	7-Isopropenylbicyclo[4.2.0]octa-1,3,5-triene-2,5-diol 7-Isopropenylbicyclo-[4.2.0]octa-1,3,5-triene-2,5-diol-5-*β*-D-glucopyranoside (3*R**,4*S**)-3,4-dihydroxy-7-methyl-3,4-dihydro-1(2*H*)-naphthalenone (3*S**,4*S**)-3,4-Dihydroxy-7-methyl-3,4-dihydro-1(2*H*)-naphthalenone 2-(1-Methylethylidene) pentanedioic acid pentanedioic acid 2-(1-methylethylidene)-5-methylester pentanedioic acid 2-(1-methylethylidene)-1-methyl ester Pentanedioic acid 2-(1-methylethenyl)-5-methyl ester 2-(1-Hydroxy-1-methyl)-2,3-dihydrobenzofuran-5-ol 2,2-Dimethylchroman-3, 6-diol 2-(3-Dihydroxy-3-methylbutyl)benzene-1,4-diol	15
	Aspergillus ochraceus	*Sargassum kjellmanianum* (b)	2-Hydroxycircumdatin C (11a*S*)-2,3-dihydro-7-methoxy-1*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11(10*H*,11a*H*)-dione Circumdatin F Circumdatin C Circumdatin D Notoamide B Selerotiamide	28

(*Contd*)

Table 3. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Number of compounds identified	Reference
	Aspergillus wentii	*Sargassum* sp. (b)	Wentiquinone C Methyl 4-(3,4-dihydroxybenzamido)butanoate 5-*O*-Methylsulochine Methyl 2-(2,6-dimethoxy-4-methylbenzoyl)-3,5-dihydroxybenzoate Methyl-2-(2,6-dihydroxyl-4-methylbenzoyl)-3-hydroxy-5-methoxybenzoate Physcion 4-(3,4-Dihydroxybenzamido)butanoic acid (*E*)-*N*-(2-Hydroxy-2-(4-hydroxyphenyl)ethyl)-3-(3-hydroxy-4-meth-oxyphenyl)acrylamide	63
	Chaetomium globosum	*Polysiphonia urceolata* (r)	Chaetopyranin 2-(2′,3-epoxy-1′,3′-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)benzaldehyde Isotetrahydroauroglaucin Erythroglaucin Parietin Asperentin 5′-Hydroxy-asperentin-8-methylether Asperentin-8-methyl ether 4′-Hydroxyasperentin 5′-Hydroxyasperentin Neoechinulin A	86
	Epicoccum sp.	*Fucus vesiculosus* (b)	4,5,6-Trihydroxy-7-methylphthalide 5-(Acetoxymethyl)-furan-2-carboxylic acid Furan-2-carboxylic acid 5-(Hydroxymethyl)-furan-2-carboxylic acid (−)-(3*R*,4*S*)-4-hydroxymellein (−)-(3*R*)-5-hydroxymellein	13
Antiplasmodial	*Ascochyta salicorniae*	*Ulva* sp. (g)	Ascosalipyrrolidinone A Ascosalipyrrolidinone B Ascosalipyrone Genistein 2,3-Dihydro-2-hydroxy-2,4-dimethyl-5-*trans*-propenylfuran-3-one	72
	Chaetomium sp.	Unknown	Chaetoxanthone A Chaetoxanthone B Chaetoxanthone C	77
Antiplasmodial; tyrosine kinase inhibitor	*Drechslera dematioidea*	*Liagora viscida* (r)	Isosativenetriol Drechslerine A Drechslerine B Helminthosporol 9-Hydroxyhelminthosporol Drechslerine C Drechslerine D Drechslerine E Drechslerine F Drechslerine G *cis*-Sativenediol Sativene epoxide (+)-Secolongifolene diol Isocochlioquinone A Isocochlioquinone C Cochlioquinone B	73
Inhibition of *β*-glucuronidase	*Aspergillus terreus*	*Laurencia ceylanica* (r)	3-Hydroxy-4-(4-hydroxyphenyl)-5-methoxycarbonyl-5-(4-hydroxy-3-formylbenzyl)-2,5-dihydro-2-furanone Butyrolactone-1 6-Hydroxymellin	57

(*Contd*)

Table 3. (*Contd*)

Bioactivity	Fungal endophyte	Algal host	Number of compounds identified	Reference
			(3*R*,4*R*)-6,7-dimethoxy-4-hydroxymellin (+)-Territonin (+)-Territonin-A (+)-Asterrelenin (+)-Terrein Oleic acid Glucopyranosyl-β-sitosterol	
Inhibition of HLE	*Coniothyrium cereale*	*Enteromorpha* sp. (g)	(–)-Cereolactam (–)-Trypethelone (–)-Cereoaldomine	21
	Phaeosphaeria spartinae	*Ceramium* sp. (r)	Spartinol A Spartinol B Spartinol C Spartinol D	40
			Spartinoxide A82775C Iso-A82775C 4-Hydroxy-3-prenyl-benzoic acid Anofinic acid	41
Protein phosphatase inhibitor	*Ascochyta salicorniae*	*Ulva* sp. (g)	Ascolactone A Ascolactone B Hyalopyrone Ascochitine Ascochital Ascosalipyrone	78
Tyrosine kinase inhibitor	*Chaetomium* sp.	*Valonia utricularis* (g)	Chaetominedione 2-Furancarboxylic acid	32
	Pestalotiopsis sp.	*Sargassum horneri* (b)	5-(Hydroxymethyl)-2-furancarboxylic acid 1β,5α,6α,14-Tetraacetoxy-9α-benzoyloxy-7βH-eudesman-2β,11-diol 4α,5α-Diacetoxy-9α-benzoyloxy-7βH-eudesman-1β,2β,11,14-tetraol	26
	Wardomyces anomalus	*Enteromorpha* sp. (g)	2,3,6,8-Tetrahydroxy-1-methylxanthone 2,3,4,6,8-Pentahydroxy-1-methylxanthone 3,6,8-Trihydroxy-1-methylxanthone 5-(Hydroxymethyl)-2-furanocarboxylic acid	14

(r), (b) and (g), same as in Table 1.

belonging to each of the major algal groups (red, green, and brown; Tables 1 and 2). *Cladosporium* has also been found from the west coast of the Shetland Islands[12].

Many studies have included macroalgal hosts only reported to the genus level (Table 1). Such reporting creates obstacles to any potential comparisons of algal hosts and their associated endophytes. Despite this, many reports have documented the common and ubiquitous occurrence of several fungal species, such as *Aspergillus* (17%) and *Penicillium* (9%), which are the most commonly isolated fungal endophytes from marine macroalgae. These two genera (*Aspergillus* and *Penicillium*) have been reported from six and eight of the locations investigated respectively (Table 1). Interestingly, several fungal endophytes that were discovered in brown algae have not been previously reported from red or green algae. Among this group of endophytes are *Acremoniella* sp., *Arthrinium* sp., *Ascotricha* sp., *Chalara* sp., *Epicoccum* sp., *Haloguignardia irritans*, *Helicosporium* sp., *Lichtheimia corymbifera*, *Monodictys putredinis*, *Oidiodendron* sp., *Pestalotiopsis* sp., *Phaeotrichoconis* sp., *Taeniolella* sp., *Tolypocladium inflatum* and *Varicosporium* sp.[9,12,13,23–26]. Also noteworthy is the large proportion of unidentified and sterile forms of endophytic fungi (30%) designated morphology-based codes for identification (Table 1). Further work is required to improve procedures for molecular identification of sterile fungal isolates, as morphological descriptions do not allow for proper documentation of the fungal biodiversity present within marine macroalgae.

Bioactivity – screening

Few studies have performed large-scale screens on the bioactivity of endophytic fungi from marine macroalgae. The work by Suryanarayanan *et al.*[9] in India represents one of the first studies that screened the chemical extracts of endophytic fungi from an array of macroalgal hosts for bioactivity (Tables 1 and 2). The majority of the

endophytic fungi tested possessed either antialgal, antimicrobial, insecticidal or antioxidant activity[9] (Table 2). Several studies have since followed[10–12], which have shown endophytes to be promising sources of bioactive natural products. The work by Ariffin *et al.*[10] resulted in the isolation of 15 endophytes from six species of macroalgae (Table 1), where over half of the fungal isolates exhibited anticancer properties, with some possessing antimicrobial activity (Table 2). Studies from the Atlantic coast of Canada[11] and the west coast of Shetland Islands[12] support the work by Suryanarayanan *et al.*[9] and Ariffin *et al.*[10], where 64 and 79 fungal endophytes were isolated respectively, and in each case, over half of the isolates obtained showed antimicrobial activity (Table 2).

Aspergillus and *Penicillium* spp. isolated from a range of hosts and locations have displayed an extensive variety of bioactivity, with numerous reports documenting antimicrobial, anticancer, anti-inflammatory, antialgal, antiinfective, antioxidant and insecticidal activity[9,16–19,27–31] (Table 2). Numerous other species have been identified, including *Alternaria* spp., *Chaetomium* spp. and *Cladosporium* spp. (Tables 1 and 2). *Alternaria* spp. extracts have shown strong bioactivity in antimicrobial and anticancer tests[9,12,23] (Table 2). Extracts from *Chaetomium* spp. have displayed a wide variety of bioactivity including antialgal, antimicrobial, anticancer and insecticidal[9,23,32]. *Cladosporium* spp. extracts have been shown to produce secondary metabolites with antimicrobial, anticancer and insecticidal activity[9,12]. *Nigrospora* spp. have been reported from a diverse array of macroalgal hosts (Table 1). Suryanarayanan *et al.*[9] have found that several *Nigrospora* spp. possess antialgal and antimicrobial activity (Table 2).

Bioactivity – natural products

The screening of endophytes from marine macroalgae has shown them to be an excellent source of bioactive natural products against a range of biological targets (Table 2). Complementing these findings are over 50 studies focused on the isolation of new natural products from endophytes of macroalgae (Table 3). Over 300 natural products have been identified from 32 endophytic fungi, with 22% of the investigated fungi being from the genus *Aspergillus* (Table 3). These 32 endophytic fungi investigated were isolated from 35 marine macroalgae (13 red, 12 brown, 7 green and 3 unidentified) with *Sargassum* spp. being the predominant macroalgae studied (Table 3). Of the natural products published, 43% (139/327) were reported as new natural product entities suggesting there is a difference in chemical diversity between terrestrial and marines endophytes (Table 3) as well as overlap. Many of the identified natural products have shown a range of bioactivity, including but not limited to, antioxidant, anticancer and antimicrobial properties (Table 3).

Conclusions

According to Overy *et al.*[33] publishing lists of marine-derived fungi based on location is only sufficient when no relationship between the location and the fungus is known. In the case of macroalgal endophytes this is almost always the case, where fungi are isolated from the inside of marine algae and the relationship between host and fungus is not known. What has developed over the recent past are either lists of endophytes from a variable list of macroalgal hosts[9,11,12] or bioassay data and chemical structures from extracts of endophytic fungi isolated from one or only a few algal hosts (Tables 2 and 3). This is not to imply that these approaches are somehow limited in impact or importance, but rather to state there is much to do in the study of endophytic fungi from macroalgae. This review attempts to summarize the current information on these two important facets of endophyte research from marine algae. Globally, endophytes have been isolated from less than 1% of the known macroalgal species resulting in a dearth of information on the abundance, distribution and species richness of endophytes from this source. Additionally, the effect of anthropomorphic influences and the nature of the relationship between macroalgae and their associated endophytes present important opportunities for research. These factors, and others, may impact a variety of endophytes and their capacity to produce novel chemical entities.

Bioassay data supports the notion that endophytes from marine algae are an important source of bioactive compounds (Tables 2 and 3), not only in terms of new natural products but also in relation to known compounds from different sources. As noted in the lack of data for distribution of endophytes, there is also a lot of work to be done in the bioassay and structure elucidation of compounds produced by algal endophytes. As a relatively new and understudied source of natural products, algal endophytes may open up a substantial vista of new chemistry. This review collates and organizes the latest literature with the aim to aid future research in the field. Clearly, there is much to do and much to discover.

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