



## Review article

## Marine endophytic fungal metabolites: A whole new world of pharmaceutical therapy exploration

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## ABSTRACT

The growing threat arises due to diseases such as cancer and the infections around the world leading to a critical requirement for novel and constructive compounds with unique ways of action capable of combating these deadly diseases. At present, it is evident that endophytic fungi constitute an enormous as well as comparatively untapped source of great biodiversity that can be considered as a wellspring of effective novel natural products for medical, agricultural and industrial use. Marine endophytic fungi have been found in every marine plants (algae, seagrass, driftwood, mangrove plants), marine vertebrates (mainly, fish) or marine invertebrates (mainly, sponge and coral) inter- and intra-cellular without causing any palpable symptoms of illness. Since evolution of microbes and eukaryotes to a higher level, coevolution has resulted in specific interaction mechanisms. Endophytic fungi are known to influence the life cycle and are necessary for the homeostasis of their eukaryotic hosts and the chemical signals of their host have been shown to activate gene expression in endophytes to induce expression of endophytic secondary metabolites. Marine endophytic fungi are receiving increasing attention by chemists because of their varied and structurally unmatched compounds that have strong biological roles in life as lead pharmaceutical compounds, including anticancer, antiviral, insulin mimetic, antineurodegenerative, antimicrobial, antioxidant and immuno-suppressant compounds. Moreover, fungal endophytes proved to have different biological activities for exploitation in the environmental and agricultural sustainability.

## 1. Introduction

There is an ever-emerging need for new and beneficial compounds attributed to the emergence of life-threatening viruses and multidrug-resistant bacteria [1]. Traditional sources of natural bioactive products that include temperate plants and soil microbes have failed to combat the observed increase in fungal infectious agents and persistent disease problems worldwide especially in immunocompromised patients such as transplanted people and cancer patients due to the use of several immunosuppressants [2, 3]. The certain microbial products appear to be distinguishing of certain biotopes, accordingly it appears that hunting novel drugs with novel modes of action should focus on organisms that reside unparalleled biotopes. In this context microorganisms of unique and unexplored ecological niches such as endophytes that inhabit such biotopes, containing marine plants (like algae, sea-grass, driftwood, and mangrove plants), invertebrates (such as sponge, corals, crustaceans,

ascidans, holothurians, and bivalves), vertebrates (mostly fish) and many other minor marine phyla are currently considered as an outstanding source of bioactive drugs [4, 5, 6, 7, 8, 9]. Fungal endophytes are a polyphyletic category of predominantly ascomycetous fungi that dwell within wholesome host tissues during at least one phase of their life cycle and without affecting any visible symptoms of disease or negative effects on their hosts [3, 10].

The endophytic community composition usually differs and is affected by numerous factors as a function of host species, host genotype, tissue origin, geography location, nutrient availability, and interactions with host as well as other abiotic and biotic stresses which result in host specificity of endophytic mycobiota of the similar host species [10]. The fungal survey of various marine invertebrates includes about 9000 species of *Porifera* (sponges), 11000 species of *Cnidaria* (jellyfish, corals, and sea anemones), 112000 species of *Mollusca*, 7000 living and 13000 extinct species of *Echinoderms*, *Arthropoda* (the prevalent phylum in the

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taxonomic system) as well as the marine plants, mainly seaweeds as well as 70 species of mangrove plants inhabiting marine environments have suggested the ubiquity of endophytes and revealed their symbiotic association in all healthy taxa studied to date [3, 10, 11, 12]. Owing to the fact that vast majority of plants and marine invertebrates or vertebrates have not been tested for their fungal endophytes, huge prospects occur for the recovery of unique fungal forms, taxa and biotypes.

Accelerating rates of ecological degradation and damage caused to terrestrial and marine ecosystems by means of climate alteration, toxic insecticides and the release of industrial effluents into such environment has managed to the loss of biodiversity mainly of plant, coral, and sponge species along with the loss of their endophytic fungal species that were not discovered until now. There may be as many as a million species of endophytic fungi alone, yet only about 100,000 have been described so far [1, 2]. The fact that new microbes are usually associated with new natural compounds makes endophytes, with their great genetic variety and undefined species, an effective tool for overcoming deadly diseases, and reducing the de-replication complications in compound discovery. Then it appears clear that prolific and trustworthy sources of bio-prospecting tested of fungal endophytes for medical, pharmaceuticals and biotechnological applications are essential for discovering new compounds of multifold importance in drug industry and human health including antibiotics, antimalarial, antiviral and anti-carcinogenesis [3, 4, 5, 6, 7]. Since the 1970's there is rising attention in endophytes and their origins, biodiversity, phytism (endophyte-host interactions), their ecological roles with a special interest toward description of their secondary metabolites due to the possibility of these microorganisms to produce a plethora of pharmacologically active natural products [6, 7, 13].

Endophytic fungi have biotechnology potential in diverse life science applications such as anticancer drugs (taxol, L-asparaginase, L-glutaminase, tyrosinase, and methioninase) [5, 6, 7, 14, 15, 16], antibacterial agents (essramycin, ayamycin, benzopyrones derivatives, and coumarine derivatives) [13, 17, 18, 19], antifungal agents (saadamycin, and prodigiosin) [20, 21], antiviral agents [4, 7] and in the biological control of various plague and contaminants [15, 22, 23]. These activities are attributed to the unique products of endophytes including steroids, alkaloids, terpenoids, quaternions, isocoumarin and quinones derivatives, phenolic, flavans and xanthenes compounds as well as peptides with pharmaceutical and biotechnology applications [1, 2, 24, 25, 26]. This review focuses on elucidating the vital role and importance of marine endophytic fungi that could open a new era for different areas of biotechnology. It also clarifies the differences in the metabolites that are produced according to differences in hosts by reviewing the structure of different metabolites derived from different marine organisms including algae, sponges and corals. It focuses on the extensive variability of biological activities associated with marine endophytic fungal metabolites and their medical and pharmaceutical applications.

## 2. Main text

### 2.1. Richness and diversity of marine-derived fungal endophytes

Although microorganisms isolated from marine environment ( $3.7 \times 10^{30}$ ) can produce numerous interesting natural compounds that are possibility drug leads, 99% of them are uncultured species [27, 28]. Because of the endophytic fungi are present in every marine organism particularly those of medical importance in clinical trials and drugs industries (Figure 1), these fungal endosymbionts represent significant and quantified constituent of fungal biodiversity that is affected by the host community diversity, structure and location [29]. The accessive competition, limited resources, and enormous selection pressure in the sea gives rise to a great prospect that marine fungal endophytic are a prolific source of unique molecular structures and bioactive compounds [30]. The surface sterilization methods that are most frequently used for endophytic mycobiome isolation are depending on the surface

disinfection of healthy host tissue samples to execute epiphytic microorganisms and then traditionally characterized using cultivation. Today, cultivation-independent molecular approaches are favored because under culture dependent methods certain endophytic fungi were not recognized due to being unamenable to culturing outside the host, growing too slowly and their morphology characteristics were very similar to others in addition to the problem of morphospecies of different groups of mycelia sterilia. Thus culture-independent methods have demonstrated greater marine endophytic fungal diversity than previously recognized [7, 27, 31, 32]. Regarding to endophytic specificity, some endophytic fungi are *Plural* species, which are commonly isolated from different types of hosts and from different fragments of the same host (wide host/tissue), and others are specific to a very narrow range of hosts (high specificity, narrow host/tissue range). *Neotyphodium* endophytes have a narrow host range, being confined to one or two plant species while indigenous abundant endophytic *Penicillium*, *Phoma*, and *Aspergillus* species cover a wide spectrum of taxonomically unrelated host species within diverse genera proposing that they progressed adaptations to overcome diverse kinds of hosts with different function roles and bioactivities [5, 7, 10, 33]. Another factors contributing to the huge variety detected in endophytic assemblages are geographical difference and host age [34]. Gao et al., suggested that specific sponge-microbe relationship was based the alteration of symbiotic fungal variety by studying the fungal diversity among two sponges from the same geographic location [33]. They reported that marine sponge *Theonella swinhoei* hosted the endophytic fungal species *Ascomycota* sp., *Fusarium* sp., *A. versicolor*, *P. chrysogenum* and *P. pinophilum* while the sponge *Phakellia fusca* hosted a higher number of endophytic fungi comprising *Ascomycota* sp., *A. candidus*, *A. fumigatus*, *A. ochraceus*, *C. parapsilosis*, *Cladosporium* sp., *Fusarium* sp., *Nigrospora oryzae*, *P. lilacinus*, *Rhizomucor pusillus* and *P. chrysogenum* [33]. Furthermore, a variety of symbiotic lifestyles can coexist between endophytes and their hosts [29]. Now we will state some of the most important marine macroorganisms which are hosted a large diversity of marine endophytic fungi. Corals are deemed as one of the ecosystems with extraordinary biodiversity in coastal oceans, and as a source for separation of fungal endophytes [35]. Couttolenc et al., reported that from different corals include *Diploria clivosa*, *Diploria strigose*, *Acropora palmate*, *Plexaura flexuosa*, *Pseudoplexaura porosa*, *Pseudotergorgia americana*, and *Sidastrea siderae*; 11 endophytic fungal genera were isolated. Among them coral derived *Fusarium* and *Curvularia* species showed the highest anti-cancer activity towards an extensive range of cancer cell lines containing breast, lunge, cervix and colon cancer cell lines [36]. Marine algae have been established to be an exceptional source of fungal endophyte. However, in the last few decades, there is an unmatched attention in produced bioactive molecules by marine algae-derived endophytic fungi [37]. Marine algilous endophytic fungi can be handled to produce compounds of medical attention. For example marine algae associated *Paecilomyces variotii* was able to produce indole derivatives with cytotoxic activity towards several cancer cell lines; red algae-endophytic *Microsporium* sp. produced physcion that caused by apoptosis in HeLa cells, endophytic *Aspergillus wentii* with *Sargassum* sp. produced wentilactone B that revealed cytotoxicity towards HeLa, HepG-2, MDA-MB-231 cell lines. Similarly, *Pestalotia* sp. derived from brown alga gave a novel chlorinated bezopenone compounds with perceivable antibiotic activity against MRSA as well as from a marine red alga *T. islandicus*, hydroanthraquinones with anti-oxidative and antimicrobial properties was isolated [11, 38, 39]. Clavicipitaceous endophytes have applied potential as biocontrol agents against insect pests of grasses, hence exploiting these naturally occurring symbioses, isolating their mycobiota to use and develop their natural products as biocides may prevent the requirement for chemical pesticides in managed grasslands [40, 41]. The clavicipitaceous fungi of concern within the *Clavicipitaceae* owned by a relatively small class of species have common characteristics in being endophytically connected with grasses as obligate biotrophic symbionts [42, 43].

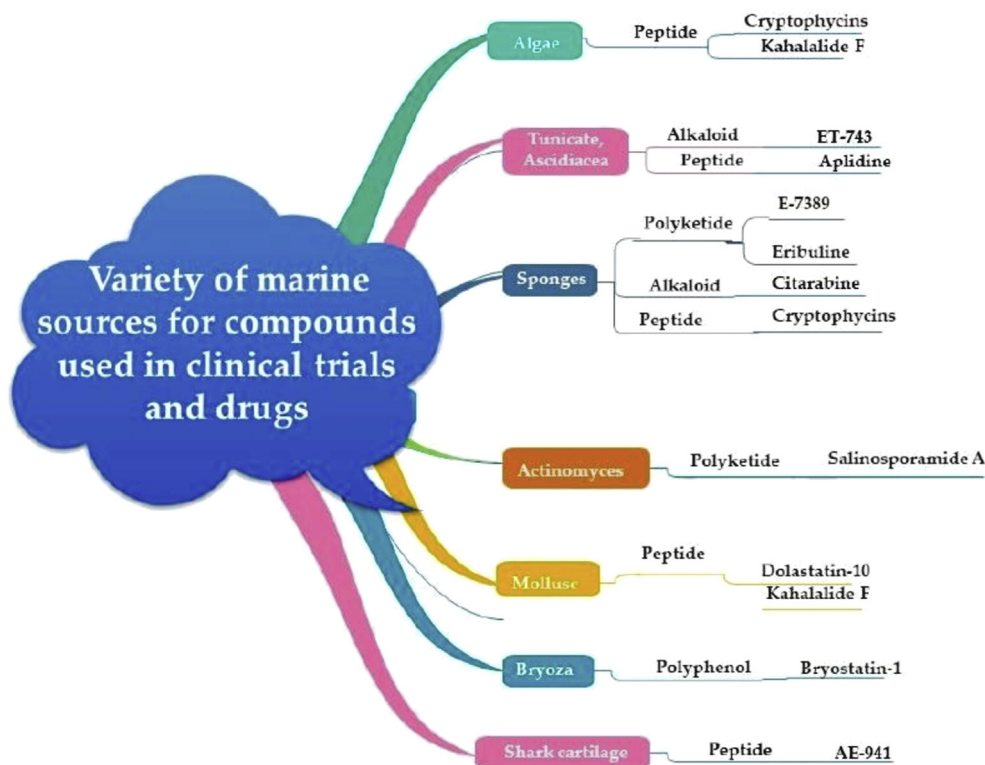


Figure 1. Marine pharmaceuticals their sources and chemical classes.

Mangrove forests represent an exclusive and dominant ecosystem consists of intertidal marine plants, commonly trees, predominantly bordering margins of tropical coastlines around the world. They provide about 70 halophytic salt tolerant plant species grow in salt coastal habitats [44]. Marine endophytic fungi from mangrove grow in habitats with distinctive conditions that attributed to the activation of fungal metabolic pathways and the diversity of the unidentified molecules produced by the endophytes [4, 45]. From 300 leaf segments of mangrove *Rhizophora mucronata* trees, 350 endophytic fungal strains were positively obtained with insecticidal, antimicrobial, antiviral, anti-inflammatory, and anti-diabetic activities [46]. Concerning endophytic fungal diversity inside mangrove plants, 96.2% belonging to the phylum *Ascomycota* which contains two types, *Sordariomycetes* and *Dothideomycetes* and 3.8% related to the phylum *Basidiomycota*. The dominating genera are *Fusarium*, *Penicillium*, *Pestalotiopsis*, *Alternaria*, *Phoma*, *Xylaria* and *Cladosporium* whereas less frequently was recorded for the genera *Periconia*, *Pithomyces*, *Diaporthe*, *Lophiostoma*, *Nigrospora*, *Phaeosphaeriopsis*, *Schizophyllum* and *Stagonosporopsis* [46]. Production of these endophytic fungal natural products supports the adaptation and survival of the fungi in mangrove plants as well as the host mangrove plant to biotic stress.

The effect of seasons, locations and plant species on the variety of fungal endophyte and secondary metabolites produced from endophytic strains were discussed [47, 48]. For example, analysis of fungal endophyte obtained from the same plant, *Terminalia* sp. collected at five different regions (India, Thailand, Eritrea, Egypt, and Cameroon) showed that the endophytic *Curvularia*, *Rhizophus*, *Chaetomium*, *Cochlonema*, *Chloridium*, *Humicola*, *Kwoniella*, *Memnoniella*, *Monocillium*, *Mycosphaerella*, *Myrothecium*, *Phialophora*, *Fusarium*, *Paraconiothyrium*, *Phoma*, *Pseudocercospora*, *Pseudofusicoccum*, *Glomerella*, and *Paecilomyces* species were obtained from the plants grown in Egypt [49], Eritrea [50], India [51], Cameroon [52], and Thailand [48]. The variation in the colonization of fungal endophytes can be described by the fact that symbiotic fungi can benefit plants by alleviating abiotic plants by pressures associated with climate change as heat and drought as well as maintaining stable

biological communities, especially despite environmental concerns [27, 53, 54]. It is obvious that biodiversity is a valuable source of innovation not only in ascertaining a plethora of up till now undefined species and their evolutionary backgrounds, genetics, ecology, and the abundance of implicit precious molecules [40]. It is a revolution of supposed an exhausted observation favorable to change sights of reductionist investigation of the past decades into snapshots of a dynamic world of systems biology [54] through elaborating combinatorial methods (microbial, chemical, and biochemical) that can lead to the discovery of bioactive agents that can be further improved based on their pharmaceutical, medicinal or other biotechnology potential [3, 4, 5, 6, 7, 13, 15, 30, 55].

## 2.2. Rationale for host and endophytes selection

Since the number of marine organisms is so large, it is important to devise creative and imaginative strategies that provide superior prospects for isolating new endophytic fungi as well as emergence of new and diverse biologically active compounds with pharmaceutical applications [30]. These strategies include; 1) searching about unique fungal sources as the deep-sea, hydrothermal vents, hyper saline water bodies and hypoxic environments, offshore waters, and oil polluted regions which are prospective to be a host for endophytes with unusual bioactive products are recommended in upcoming years [31], 2) the culture-independent molecular technique and meta-genomic method aim to reveal microbial variety, particularly real symbioses that can be gained through vertical transmission among generations [47], 3) the progress of new isolation method copying the natural environments to obtained new symbiosis particularly uncultured symbiotic fungi and great-flux screening procedure for assaying the biological activity [4,6,23], 4) successful isolation approach for trace natural compounds and great-flux selection procedure for assaying the biological activity [56], 5) selection about gene cluster participates in the biosynthesis of significant pharmaceutical and medical metabolites and detection of biosynthesis mechanisms [1, 2, 27], and 6) heterologous expression of

pharmacological metabolites of uncultured symbiosis and huge scale productivity of natural compounds [3, 41].

### 2.3. Diversity of products isolated from the marine endophytic fungi

Because of the rapid increased risk of developing several types of cancer and infectious agents (bacteria, fungi, and viruses) that possess resistance to conventional drugs, there is great demand for exploring new drugs of new structures [1, 2]. The oceanic environment covers above 70% of the planet's surface and it is a residence to an enormous diversity of organisms. However, as a result of the extreme profundity of the oceans, they appear in excess of 99% of our planet's natural habitation; providing almost unlimited resources for new natural products compared to the terrestrial habitation up to 100 m [45,57]. Each marine plant, animal, and microorganism produces huge number of metabolites with unique feature of lead structures that have promising prospects as novel drugs for treating cancer, inflammation, and infection as well as these compounds cannot be found in terrestrial habitats [9, 56, 58]. Many of marine metabolites derived from sponges, snails, worms, tunicates, molluscs, soft corals, and their symbiotic microorganisms are in clinical phase trials (Phase I, Phase II or Phase III; Table 1) or approved as drugs in the zone of cancer, pain, viral and wound healing diseases [28, 31, 59, 60]. Interestingly, the main problem with marine natural products are insufficient quantities of most of the biomass of marine macro-organisms in nature, especially sponges; soft corals; coral reefs or seaweeds, and thus their deficiency often causes difficulties in supplying sufficient quantities of their effective compounds for drug improvement and sustainable production [8, 61, 62].

Actually, marine microorganisms such as fungi often occur inside every possible marine habitat. The presumption concerning the powerful symbiotic correlation between host and its microorganisms has been growingly solidified. Moreover, recent research has indicated that the isolated bioactive compounds from sponges, sea fountains, corals, etc., may have already been created by their own endophytic microorganisms in the host-endophyte relationships during colonization [30, 33]. Marine fungal endophytes have displayed to be potential sources of bioactive secondary metabolites [3, 55]. The antibacterial agents ayamycin, esramycin, benzopyrone derivatives, and isocoumarin derivatives [13, 17, 18, 19]; antifungal agents include prodigiosin and saadamycin [20, 21] and anticancer agents as taxol, L-asparaginase, lovastatin, tyrosinase, methionimase, and L-glutaminase [5, 6, 14, 15, 16, 45, 63, 64] were isolated from endophytic microorganisms obtained from different marine sponges and corals. Also, antifungal and cytotoxic polyoxygenated steroids (penicisteroids A, and B), anthraquinone, cyclopentanone, and naphthoquinone derivatives were obtained from the marine seaweeds [33, 57] as well as isobenzofuranone derivative, marilones A-C, stachylines A-D, and marilines A-C with antioxidant properties were gotten from the algicolous fungus *Epicoccum* sp., as well as the sponge-derived *Stachyldium* sp. [11, 38, 65, 66].

Endophytic fungi of these marine macroorganisms algae, sponges, corals, and mangrove have been the subject of this review since they are promising sources of diverse endophytic fungi with an isolation rate of 17%, 12%, 10%, and 10%, respectively as illustrated in Figure 2 [67]. Overall, from Figure 3 we can assume that the alkaloids and terpenoid constitute the highest percentage of compounds in the bioactive constituents of marine endophytic fungi followed by macrocyclic lactones, steroids, phenyl propanoid, anthraquinones, azaphilones, phenyl ether derivatives, and peptide as well as in this order they are the most frequent fungi in the isolation procedure. However when comparing the ratio of new compounds to the known compounds within each group of these chemical classes, we find that the ratio of new compounds is highest in azaphilones and then phenyl propanoid, macrocyclic lactones, and terpenoid while the ratio of new compounds to the reisolated known compound was the least in alkaloid related compounds and phenyl ether derivatives. These metabolites have a heterogeneous array of physiological characteristics and many of them are previously unexplored in

nature such as esraamycin which was the first triazole pyrimidine in nature and ayamycin which has an unusual chlorinated structure [17, 18, 68].

### 2.4. Endophytic fungi as factories of functional pharmaceutical metabolites

Several marine endophytic fungi have been stated as producers of antibacterial, antifungal, antiviral, antitumor and antioxidant activities. For example, El-Gendy et al. isolated and evaluated the different biological activities of marine fungal endophytes among them 11 strains produced enzymatic inhibitory activities against several enzymes [7]. Since these enzymes are involved in several diseases as diabetes, cancer, and unwanted skin pigmentation, their inhibitors are important medicines. Moreover, *F. oxysporum* MERVA39, *Lophiostoma* sp. MERVA36, *P. chrysogenum* MERVA42, *A. arundinis* MERVA22, and *A. versicolor* MERVA29 exhibited great antibacterial activity against different G-positive and G-negative bacteria [7]. On the other hand, the extracts of *D. rudis* MERVA25, *A. alboluteum* MERVA32, *P. polonicum* MERVA43, and *T. harzianum* MERVA44 showed potent antifungal activities against different fungi (*A. flavus*, *C. albicans*, *C. tropicalis*, *M. canis*, *T. mentagrophytes*, *T. rubrum*, and *G. candidum*) [7]. Xu et al. reported that among over 700 compounds obtained from 105 marine fungal isolates (most of them were from *Aspergillus* and *Penicillium*); 285 compounds (40%) showed antimicrobial activities, of which 116 (15%) were new antimicrobial structures [69]. These biological activities are attributed to the ability of endophytic fungi to produce different varieties of chemical classes belonging to swinholide, theopalauamide, bryostatin, pederin, mycalamide, mazamine, onnamide, alkaloids, steroid, flavonoid, terpenoid, tannins, and coumarines [3, 31, 56, 70, 71].

### 2.5. Chemical variety and biological function of products from marine fungal endophytes

#### 2.5.1. Bioactive metabolites from marine fungal endophytes of algae

The association between the host and its endophytic fungi displays symbiotic features as the endophytic inhabitant frequently gains nutrients from the host and in return strongly promotes algal growth and improves its fitness through producing definite efficient metabolites [42]. Several species of macroalgae have been tested universal in relation to their connected fungal populations, which contains different genera since the union concerning fungi and marine algae stimulates the biosynthesis of metabolites with curative possibility by these fungi [72]. Amongst these metabolites, the most frequently isolated chemical classes are peptides, polyketides, lactones, alkaloids and terpenes. With regard to the functional metabolites previously obtained from endophytes algicolous fungus, we can focus on a superior structural assortment and bioactivity of natural products, such as the new phenalenone derivatives (1–7) which were derived from endophytic *Coniothyrium cereal* of the green algae *Enteromorpha* sp. with varied activities. Compound 5 showed antibacterial activity towards *S. aureus* because of the existence of a diketo-lactone circle in its structure but structures 2, 4 and 7 showed antagonistic activity against *Mycobacterium phlei* [73]. Structures 1 and 5 displayed effective inhibition of leukocyte elastase (HLE) (Figure 4a).

Moreover, the novel compounds spartinol A (8, showing weak inhibition of leukocyte elastase, HLE), B (9), C (10), and D (11) were obtained from *Penicillium* sp. associated with marine *Phaeosphaeri spartinae* (Figure 4a) [73]. Novel citrinal A (12) with cytotoxic effects on the A-549 and HL-60 cell lines was obtained from endophytic *Penicillium* sp. of *Blidingia minima* [74]. Ascosalipyrrolidinone A (13) was isolated from *Ascochyta salicorniae*, the endophytic fungus of *Ulva* sp. (Figure 4a) [75]. Ascosalipyrrolidinone (13) is an alkaloid compound that has antiplasmodial activity towards *P. falciparum* K1 and NF 54, as well as antimicrobial and p56lck tyrosine kinase inhibiting activity. Norditerpenoids derivative (14) from *Aspergillus wentii* EN-48, an algicolous endophyte of *Sargassum* sp., expressed cytotoxicity towards several human tumor cell lines. The anticancer agent cytoglobosins C and D (15) were obtained



**Table 1.** List of clinical and natural products isolated from marine sources with potential drugs applications.

Medical status	Compound name	Structural class	Molecular Target	Host	Disease area
Approved	Cytarabine, Ara-C	Nucleoside	DNA polymerase	Sponge	Cancer (Leukemia)
	Viderrabine, Ara-A	Nucleoside	Viral DNA polymerase	Sponge	Antivirals (Herpes simplex)
	Ziconotide	Peptide	N-type Ca channel	Snail	Ache (Chronic pain)
	Eribulin Mesylate (E7389)	Macrolide	Microtubules	Sponge	Sarcoma (breast cancer and liposarcoma)
	Citarabine	Alkaloid	Inhibition of DNA synthesis	Sponge	Leukemia (acute non-lymphoblastic)
	Omega-3-acid ethyl esters (Lovaza <sup>®</sup> )	Omega-3 fatty acids	Trygliceride-synthesizing enzymes	Fish	Hypertriglyceridemia (Pancreatitis)
	Trabectedin (ET-743)	Alkaloid	Minor groove of DNA	Tunicate	Malignance (Breast, prostate, and paediatric sarcomas)
	Eribulin (E7389)	Polyketide	Inhibition of growth phase of microtubules without affecting the shortening phase and sequesters tubulin into nonproductive aggregates	<i>Lissodendoryx</i> sp. <i>Halichondria okadaei</i> , Sponge	Advanced solid tumors, breast
	Phase IV	Actinomycin/	Peptide	Inhibition of RNA polymerase	<i>Streptomyces parvullus</i> , <i>Streptomyces</i> sp. <i>ZZ338 Actinomyces</i>
Phase III	Brentuximab vedotin (SGN-35)	Antibody drug conjugate (MM auristatin E)	CD30 & microtubules	Mollusk	Sarcoma (Hodgkin lymphoma)
Phase III	AE-941/	Peptide	Inhibition of gelatinolytic and elastinolytic activities of MMP-2, MMP-9, and MMP-12.	Shark cartilage	Renal, lung cancer
Phase II	Plitidepsin (Aplidin <sup>®</sup> )	Depsipeptide	Rac1 & JNK activation	Tunicate	Cancer (Acute lymphoblastic leukemia)
	Dolastatin 10/	Peptide	Inhibition of microtubules and pro-apoptotic effects	<i>Dolabella auricularia</i> , Mollusc	Pancreatic cancer
	DMXBA (GTS-21)	Alkaloid	$\alpha$ 7 nicotinic acetylcholine receptor	Worm	Cognition/Schizophrenia (Alzheimer's disease)
	Plinabulin (NPI-2358)	Diketopiperazine	Microtubules and JNK stress protein	Fungus	Sarcoma (Non-small-cell lung carcinoma)
	Elisidepsin (Irvalec <sup>®</sup> )	Depsipeptide	Plasma membrane fluidity	Mollusk	Tumor (Breast, colon, pancreas, lung, and prostate cancer)
	Aplidine	Peptide	Induce the apoptotic cascade	<i>Aplidium albicans</i> , Tunicate, Ascidiacea	Leukemia Non Hodgkin Lymphoma
	PM1004 (Zalypsis <sup>®</sup> )	Alkaloid	DNA-binding	Nudibranch	Tumor (Solid human tumors and hematological malignancies)
	Eribulin (E7389)	Polyketide	Lissodendoryx sp. <i>Halichondria okadaei</i> , Sponge	Advanced solid tumors, breast	Activation of cellular apoptosis under anchorage-independent and -dependent cell culture conditions
	CDX-011 Marizomib	Antibody drug conjugate (MM auristatin E)	Glycoprotein NMB & microtubules	Mollusk	Tumor (Breast cancer)
	Bryostatin-1/	Polyketide	Inhibition of growth and alteration of differentiation	<i>Bugula neritina</i> , Bryozoa	Metastatic solid tumors
Phase I	(Salinosporamide A: NPI-0052)	Beta-lactone- lactam gamma	20S proteasome	Bacterium	Sarcoma (Multiple myeloma)
	PM01183	Alkaloid	Minor groove of DNA	Tunicate	Sarcoma (Myeloid leukemia cells)
	Kahalalide F	/Peptide	Induction of changes in lysosomal membrane	<i>Elysia rufescens</i> , <i>Mollusc</i> / <i>Bryopsis</i> sp., Macroalgae	Prostate cancer
	SGN-75	Antibody drug Conjugate (MM Auristatin F)	CD70 & microtubules	Mollusk	Sarcoma (Renal cell carcinoma)
	PM02734/e	Peptid	Antiproliferative	<i>Elysia rufescens</i> , Mollusk	

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Table 1 (continued)

Medical status	Compound name	Structural class	Molecular Target	Host	Disease area
					Breast, colon, pancreas, lung and prostate
	ASG-5ME	Antibody drug Conjugate (MM) Auristatin E	ASG-5 & microtubules	Mollusk	Sarcoma (Pancreatic, prostate and gastric cancers)
	Hemiasterin (E7974)	Tripeptide	Microtubules	Sponge	Sarcoma (Antimitotic and antineoplastic)
	Bryostatin 1	Polyketide	Protein kinase	Bryozoa	Sarcoma (Anti-AIDS/HIV)
	Salinosporamide A (Marizomib <sup>®</sup> ) (NPI-0052)	/Polyketide	Prevention of proteins breakdown involved in signal transduction, which blocks the cancer cells growth and survival	<i>Salinospora tropica</i> , <i>Actinomyces</i>	
	Pseudopterosins	Diterpene glycoside	Elcosanoid metabolism	Soft coral	Wound healing (Anti-inflammatory and analgesic activity)

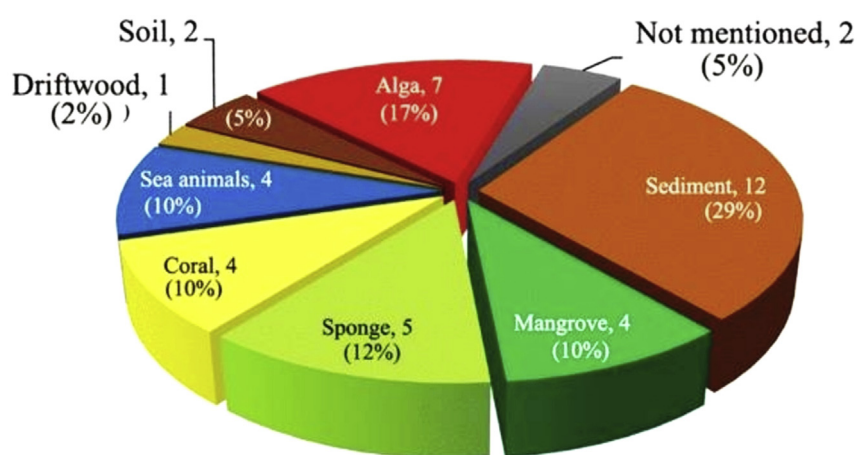


Figure 2. Distribution of marine-derived fungal endophytes and isolation rate among different marine sources.

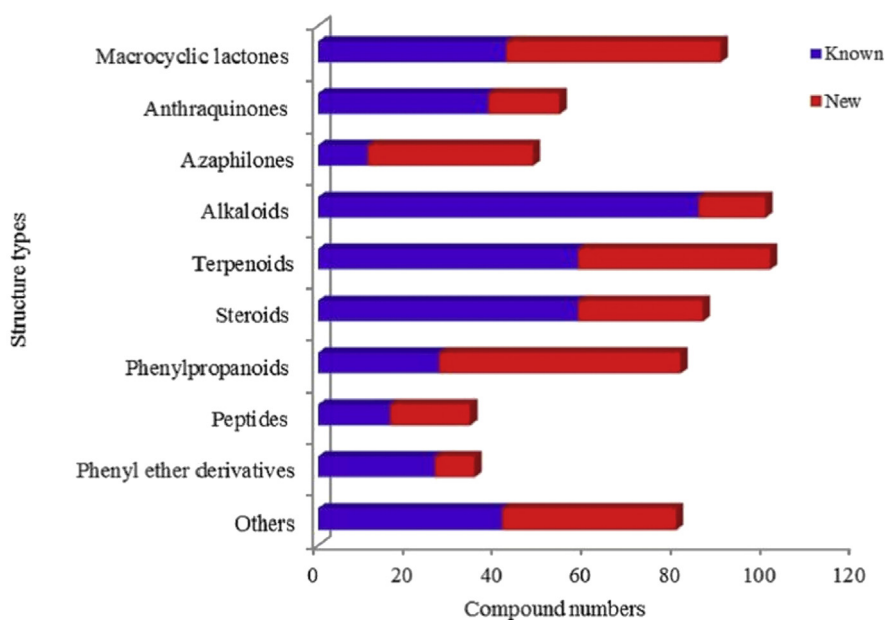


Figure 3. Distribution ratio of different chemical metabolites in endophytic natural products obtained from marine fungal endophytes.

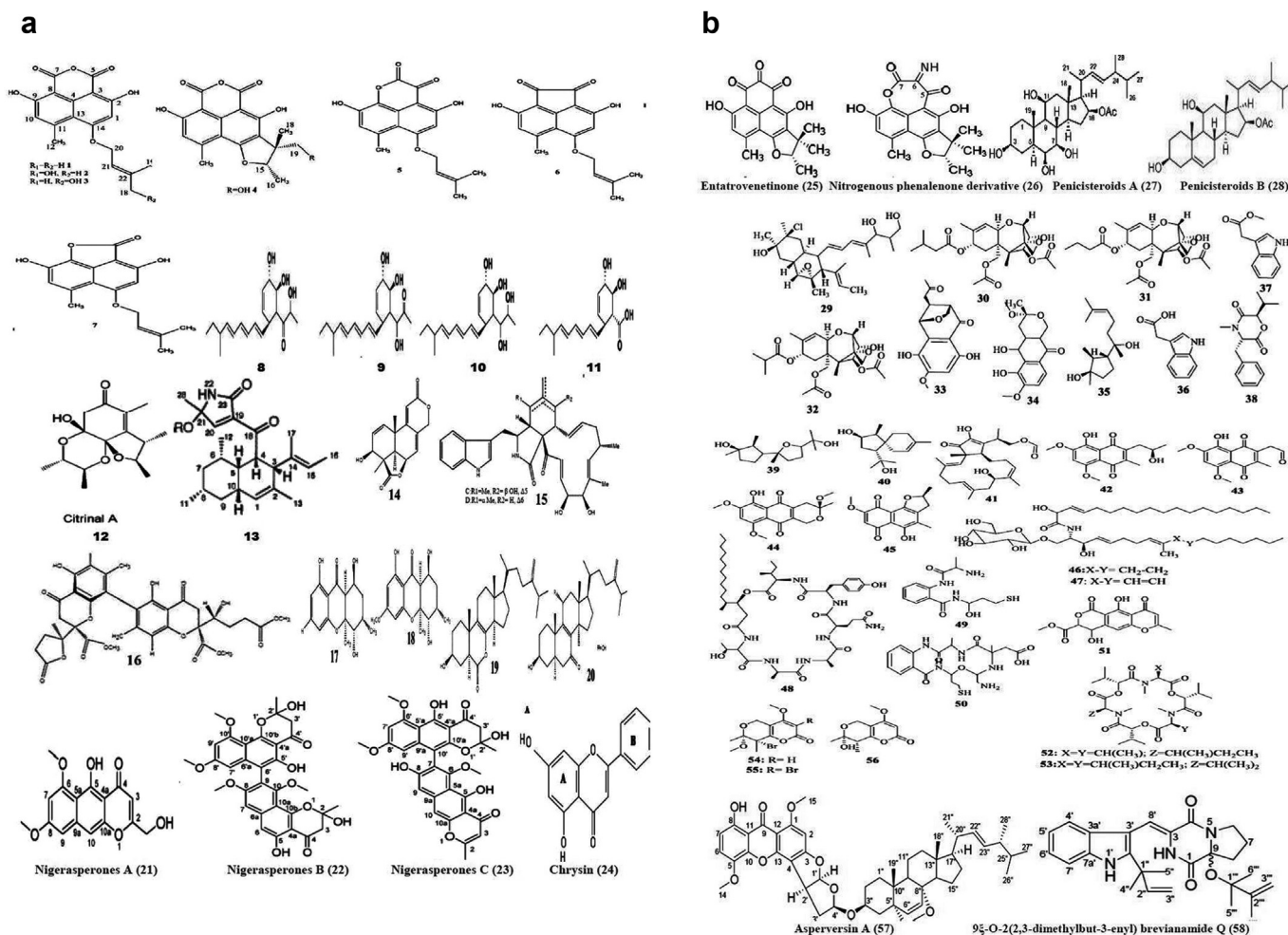


Figure 4. Secondary metabolites from marine fungal endophytes of algae.

from *Chaetomium* sp. while the polyketide, noduliprevenone (16), obtained from an algicolous fungus, *Nodulisporium* sp. Algicolous xanthone derivative, monodictysin B and C (17 and 18) of algicolous *Monodictys putredinis* exhibited equinoctial activity as inducers of NAD (P) H: quinone reductase (QR) in cultured mouse Hepa 1c1c7 cells (Figure 4a).

Moreover, compounds 19 and 20 have been extracted from the endophytic *Aspergillus ochraceus* of *Sargassum kjellmanianum* with cytotoxic activity towards NCI-H460 and SMMC-7721 cancer cell lines [76]. Three novel naphtho-g-pyrones; nigerasperone A (21), nigerasperone B (22), nigerasperone C (23) were categorized from a fungal endophyte *A. niger* EN-13 derived from marine brown alga *Colpomenia sinuosa* with weak inhibitory effects towards A-549 and SMMC-7721 cell lines, little antifungal activity towards *C. albicans*, and medium activity on DPPH scavenging activity (Figure 4a) [77, 78]. Chrysin (24) isolated from *Chaetomium globosum* of green alga *Chaetomorpha media* exhibited activities on MCF-7 cells, G2M phase cell cycle arrest, MMP loss in MCF-7 cells and ROS production [38]. Entatrovetinone (25) and the unusual nitrogenous phenalenone derivative (26) were obtained from marine endophytic fungus *C. cereale* obtained from the Baltic sea algae *Enteromorpha* sp. Compound 26 displayed a medium cytotoxicity towards K562, SKM1 and U266 cancer cell lines (Figure 4a and b) [79].

Two novel penicisteroids A (27) and B (28) were gotten from the extract of endophytic *P. chrysogenum* QEN-24S derived from the marine red algae *Laurencia* sp. but only penicisteroid A (27), exhibited strong antifungal and cytotoxic activities (Figure 4b) [80]. Fungal Endophytes of the genus *Fusarium* have been stated for the construction of structurally unique and complex yields having different important biological

activities as antiviral, anticancer, antiparasitics, immunosuppressants, immunomodulatory, antithrombotic, antioxidant, antimalarial, and enzyme inhibitory activities [81]. For example compound 29 to compound 65 were isolated from marine endophytic *Fusarium* species. Fusarielin E (29), T2-toxin (30), 8-n-butyrylneosolaniol (31) and 8-isobutyrylsolaniol (32) showed antifungal activity; while compounds 33 and 34 showed antibacterial activity towards *Mycobacterium tuberculosis* (Figure 4b) [81, 82]. On the other hand, structures 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46 and 47 were isolated from different marine fungal endophytes of algae (Figure 4b). On the other hand, fusarithioamide A (49) showed potent toxicity with MIC 1.9–7.8 µg/mL [83] but fusaripeptide A (48) showed strong antifungal activity with MIC 0.11–0.24 µM [84, 85].

Interestingly, new aminobenzamide derivative fusarithioamide B (50) revealed a broad range of antimicrobial activity towards *C. albicans*, *S. aureus*, *E. coli* and *B. cereus* [86, 87]. Lateropyrone (51), enniatins B1 (52), and A1 (53), bromomethylchlamydosporols A (54), and B (55) as well as chlamydosporol (56) exhibited activity towards sensitive and resistant strains of *S. aureus* (Figure 4b). However, fusaripeptide A (48) showed important antiplasmodial activity against *P. falciparum* [88]. Similar significant consideration has been paid to endophytic *Aspergillus* species derived from algae, due to their capacity to yield new metabolites with effective bioactivities. Two novel structures, 57 and 58 were yielded from endophytic *A. versicolor* of marine brown alga *Sargassum Thunbergii*. Both of them showed lethal activity towards *Artemia salina* [89]. These compounds and literatures indicated that the marine algal-derived fungal endophytes are abundant resources of novel bioactive products.

### 2.5.2. Bioactive metabolites from marine fungal endophytes of sponge

One of the oldest metazoan animals is sponges (*Phylum porifera*) providing classic examples of microbial macro-faunal partnerships [90]. Generally, for great quantity of fungal biomass in sponge tissues, microbes can contribute over 40–70% of the sponge mass [30, 91]. It should be noted that sponges are well known as a primary fountainhead for drug development, and that many of their medicinal compounds were subsequently isolated from their endophytic fungi, which reinforced the hypothesis that endophytic fungi are the true producers of these metabolites and some natural products of marine invertebrates originated from their microbial endophytes [8].

Due to the diversity of species and the widespread distribution of sponges, marine sponges, and soft corals represent a wealthy reservoir of marine fungal diversity, and some not isolated until now have the capability to yield diverse metabolites with the prospective to utilize as pharmaceuticals or pharmaceutical leads [33]. This interest was primarily driven by the increasing number of therapeutically active compounds extracted from endophytic fungi of marine sponges such as the previously un-described twenty one secondary metabolites with varied chemical structures including neoaustrin-type meroterpenes (citronigrin A; **59** and citronigrin B; **60**), austinoneol type meroterpenes (citronigrin C; **61** and citronigrin D; **62**), preaustrinoid A-type meroterpenes (citronigrin E; **63**) and paraherquonin-type meroterpenes (citronigrin G; **64**, citronigrin I; **65**, citronigrin F; **66** and citronigrin H; **67**) that were obtained from one marine endophytic fungi, *Penicillium citronigrum*, derived from sponge *Pseudoceratina purpurea* obtained from Indonesia (Figure 5a) as described by Rusman [92]. Out of these previously undescribed natural products of different structures, citronigrin B (**60**) inhibited protein kinases [92]. Moreover, structures **68**, **69** and **70** were extracted from the cultures of endophytic *A. niger* derived from the sponge *Axinella damicornis* (Figure 5a). In biological tests, the novel aflavinine derivative displayed activity towards *B. subtilis*, *S. epidermidis* and *S. aureus* along with cytotoxicity toward HeLa, L-5178Y and PC-12 cell lines [92].

Furthermore an extensive range of metabolites were obtained from fungus *Stachylidium* sp. derived from sponge, containing marilonones (unusual phthalides **71–75**) and stachylines A–D (**76–79**) [65,66,93] with interesting biomedical activities from only one endophytic fungal isolate (*Stachylidium* sp.) that proved that sponge derived endophytic fungi are a whole new world of pharmaceutical and medical therapy exploration field (Figure 5b). Interestingly, marilone (**75**) was evaluated in a panel of 44 psychoactive receptors, containing 11 serotonin receptors, and it displayed specific antagonistic effect on the serotonin receptor 5HT<sub>2B</sub> as well as marilone (**71**) revealed inhibition ability against the cannabinoid receptor CB<sub>2</sub> (K<sub>i</sub> = 5.97, and 5.94 μM, respectively) [30, 93]. The Polyketide red pigments glycyrlubropunctatin (**80**), N-threoninerubropunctamine (**81**), N-glutarylrubropunctamine (**82**) and monascorubramine (**83**) were isolated and identified from the endophytic ascomycetous fungi *Talaromyces verruculosus*, *Trichoderma atroviride*, and *Aspergillus sydowii* with potential anticancer and antioxidant activities (Figure 5b) [94].

In addition, a rare compound number **84** was extracted from culture of fungus *B. bassiana* TPU942, derived from sponge obtained from Iriomote Island in Okinawa, with structures chrysazin (**85**) and globosuxanthone A (**86**) (Figure 5b) [95]. These compounds (**84–86**) were examined for their antimicrobial activity towards *Mucor hiemalis*, *C. albicans*, *S. aureus* and *E. coli* as well as cytotoxicity towards HCT-15 and T-cell cancer cell lines, compounds **85** and **86** exhibited antifungal towards *C. albicans* but only compound **86** repressed the HCT-15 and Jurkat cells proliferation. The isolation of compounds **87**, **88**, **89**, **90**, **91** and **92** from *E. chevalieri* MUT 2316 derived from the sponge *Grantia compressa* in solid culture condition in addition to asperflavin (**93**), cinnalutinin (**94**), cyclo-L-trp- l-ala (**95**) under liquid culture (Figure 5b, c) were reported [24]. Compound (**89**) showed antibacterial and antimicrobial activity as well as inhibitory activity against tyronisase, at lower concentrations then this compound can be applied as commercial

antifouling formulations. Compounds **89** and **90** presented a broad-spectrum activity and they are being to be a common biocide. A formulation composed of the structures **89**, **90** and **95** are capable to contrast the growth and adhesion of all examined bacteria. Similarly, compounds **88**, **90** and **95** are capable to prevent the growth and adhesion of all examined microalgae.

The endophytic fungus *Daldinia eschscholtzii* obtained from an Indonesian sponge *Xestospongia* sp. obtained from Indonesia was found to yield new glycosylated aromatic chromanone-type structure; karimanone (**96**), with three related compounds (**97**, **98** and **99**, Figure 5c) [91]. All structures were active towards a multidrug-resistant strain of *S. enterica* ser. *Typhi*. In addition, four benzofurans; penicifurans A–D (**100–103**) were extracted from culture of fungal endophyte *Penicillium* sp. MWZ14-4 (Figure 5c) [96]. Penicifuran A (**100**) exhibited inhibitory activity towards *S. albus* [96]. Four compounds **104**, **105**, **106** and **107** were obtained from fungus *P. sclerotiorum* (Figure 5c) [97]. Compound **104** demonstrated antiviral activity towards HSV and EV71 [97].

Intriguingly, Cao et al., isolated 101 terpenoid related compounds containing 43 novel structures from the marine invertebrates and their symbiotic microorganisms. These new compounds showed antibacterial, cytotoxic and antifouling activities [98, 99]. Four novel bisabolane-form sesquiterpenoids were separated from the extract of *Aspergillus* sp. (ZJ-2008004) associated with the sponge *X. testudinaria*, including compounds **108**, **109**, **110** and **111** (Figure 5c) [100]. Compound **109** showed powerful inhibitory activity towards *S. albus* and *M. tetragenus* and compound **111** was active against *S. albus* and *B. subtilis* as well as **110** exhibited powerful preventing activity towards four pathogenic bacteria *B. subtilis*, *S. lutea*, *E. coli* and *M. tetragenus* as well as exceptionally towards two marine bacteria (*V. parahaemolyticus* and *V. anguillarum*) (MIC = 2.50 μmol/L for all) [100].

In addition the unreported compounds pyripyropene derivatives; **112** and **113**, previously described pyripyropenes including compounds **114**, **115**, **116** and **117** (Figure 5d) were obtained from the fungus *F. lateritium* 2016F18-1. Structures **114**, **116** and **117** revealed important cytotoxicity towards five human cancer cell lines; but structures **115** and **117** revealed important cytotoxicity towards Sf9 cells [99]. Purpurogemutantin (**118**), macrophorin A (**119**) and 40-oxomacrophorin (**120**) were isolated from endophytic *Gliomastix* sp. ZSDS1-F7 derived from sponge *P. fusca* obtained from the Yongxing island of Xisha, China (Figure 5d). Structures **118–120** exhibited in vitro important cytotoxicity towards various cancer cell lines. Also, structures **119** and **120** showed a medium antitubercular activity [101]. Beside the epoxyphomalins A (**121**) and B (**122**) as well as epoxyphomalins C (**123**), D (**124**) and E (**125**) were obtained from the extract of the fungus *P. sporulosum* derived from the sponge *E. perox* collected from the Caribbean sea (Figure 5d). Structures **121** and **122** showed effective anti-proliferative activity towards a panel of 36 human tumor cell lines as well as compound **124** exhibited selectively cytotoxicity, specially towards the prostate PC3M and bladder BXF 1218 L cancer cell lines [35].

### 2.5.3. Bioactive metabolites from coral derived fungal endophytes

Coral reefs are the greatest productive ecosystem and the source of a wide range of bio-synthetic products that are structurally unique. The microorganisms connected with coral reefs have been explained as a distinguishing source for novel active metabolites [28, 35]. Ten anthraquinone derivatives (**126–135**) were extracted from the culture of *Alternaria* sp. ZJ-2008003 derived from *Sarcophyton* soft coral obtained from the South China sea, containing four novel tetrahydroaltersolanols C–F (**126–129**), dihydroaltersolanol A (**130**) and five new alterporriols N–R (**131–135**) (Figure 6a) [102]. Compounds **126** and **134** showed antiviral activity towards the porcine reproductive and respiratory syndrome virus (PRRSV). Compound **133** displayed cytotoxic activity towards the PC-3 and HCT-116 cell lines [102]. Azaphilone derivatives (**136–142**) were obtained from fungal strain *P. pinophilum* XS-20090E18 derived from the gorgonian corals, isolated from the Xisha Islands, containing three novel pinophilins D–F (**136–138**), with four known



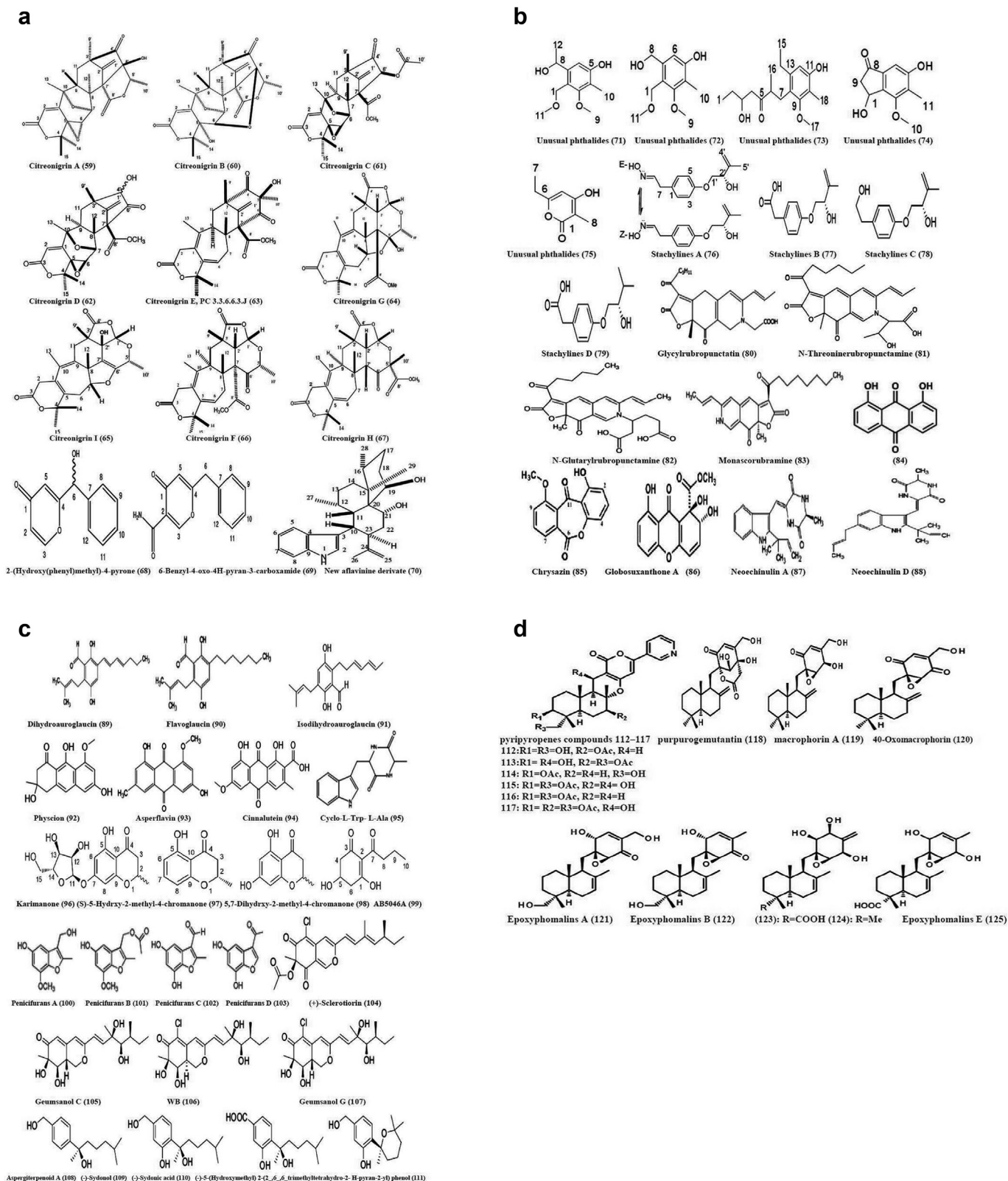


Figure 5. Secondary metabolites from marine fungal endophytes of sponge.

azaphilone derivatives (pinophilin B; 139, (–)-mitorubrin; 140, (–)-mitorubrinol; 141 and (–)-mitorubrinic acid; 142) [103]. Compound 143 was obtained from fungus *Pestalotiopsis* sp. and revealed effectively and selectively antiviral activity towards enterovirus 71 (Figure 6a) [104]. From fungus *Scopulariopsis* sp. derived from the

gorgonian corals; three alkaloids structures containing a monoterpenoid moiety (144, 145 and 146) and three compounds 147, 148 and 149 were isolated (Figure 6a and b) [105]. All of these compounds except 149 displayed effective anti-larval settlement activity towards *B. Amphitrite*.

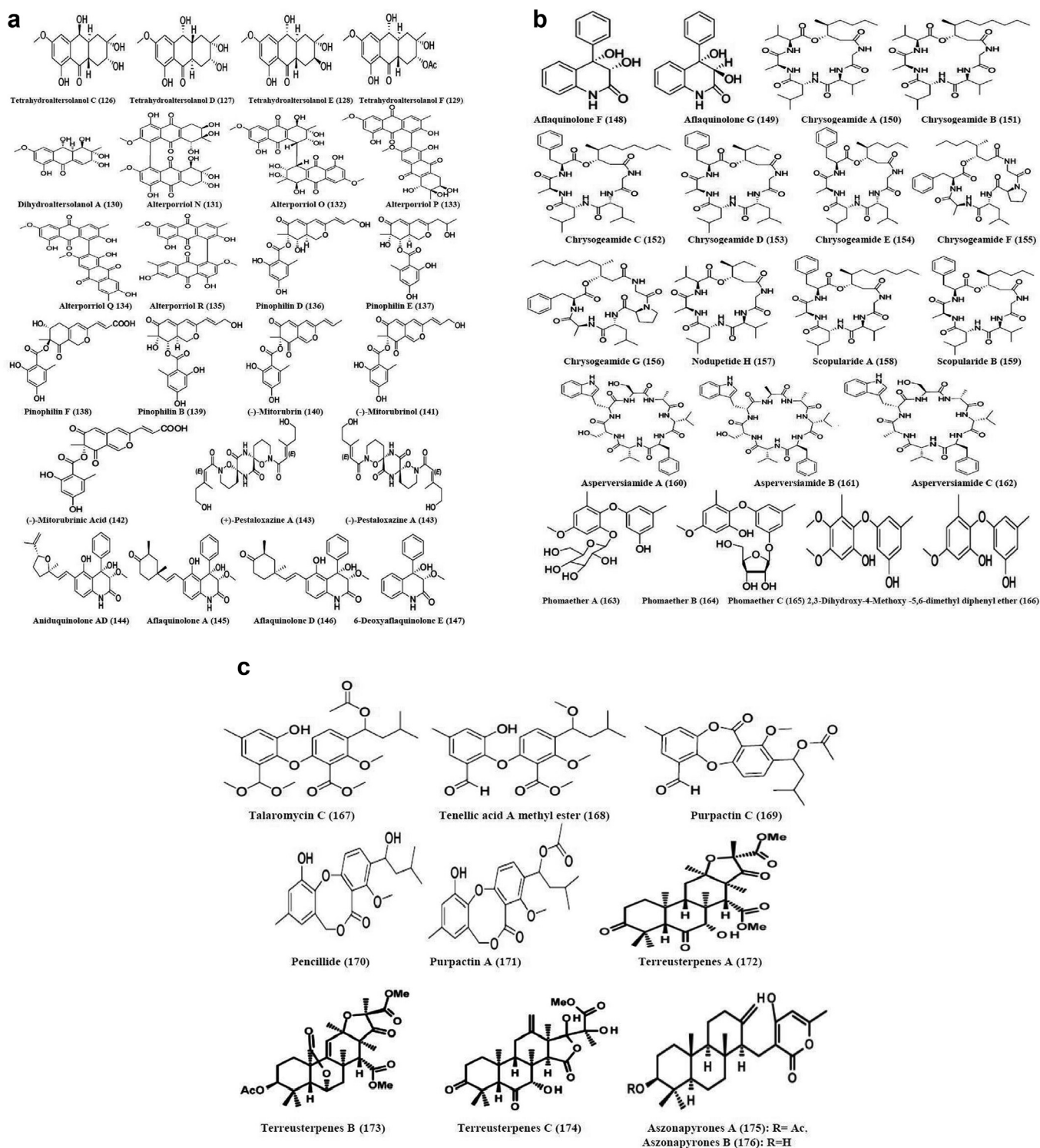


Figure 6. Secondary metabolites from marine fungal endophytes of corals.

In specific, compound 144 revealed highly powerful antifouling activity towards *B. amphitrit*.

Regarding to the peptide related compounds, ten cyclohexadepsipeptides were produced by fungus *P. chrysogenum* (TA01-16) derived from the gorgonian corals, containing the novel structures chrysogeamides A-C (150–152) and chrysogeamides D-H (153–157) as well as the identified structures 158 and 159 (Figure 6b) [106]. Compounds 150–154 exhibited discriminating activity in promoting angiogenesis towards the Tg (Flk1: EGFP) transgenic zebra fish *D. rerio* embryo

[106]. By using molecular networking methods, three novel aspersersiamides A-C (160–162) were obtained from fungus *A. versicolor* (CHNSCLM-0063) (Figure 6b) [106]. These compounds 160, 161 and 162 revealed effectively inhibitory activity towards *M. marinum*, proving respected application in handling *M. marinum* infection [106]. Also, two new diphenyl glycosides, phomaethers A-B, (163 and 164), novel phomaether C (165) and identified compound 166 were extracted from fungus *Phoma* sp. derived from gorgonian corals (Figure 6b) [107]. Compounds 163, 164 and 165 exhibited potent antibacterial activity,

representing that they might be established as favorable antibacterial agents. Besides other phenyl ether derivatives such as **167**, **168**, **169**, **170** and **171** isolated from different endophytic fungi derived from different marine gorgonian soft corals as well as revealed antilarval settlement activity towards *B. amphitrite* (EC<sub>50</sub> = 2.2–4.8 µg/mL) and cytotoxic activity towards HepG2, MCF-7/ADR, HCT-116, Hep3B and PC-3 cell lines (IC<sub>50</sub> = 4.3–9.8 µmol/L) (Figure 6c) [103, 108].

Moreover, terreusterpenes A-C (**172–174**, Figure 6c) were obtained from the extract of *A. terreus* isolated from soft coral *S. subviride* obtained from the Xisha Island, China. Structures **172** and **173** showed effective inhibitory activity towards BACE1 [109]. Aszonapyrones A (**175**) and B (**176**) were obtained from fungus *N. laciniosa* KUFC 7896. Structure **175** showed effective antibacterial activity towards *S. aureus* ATCC 25 and 923 as well as *B. subtilis* ATCC 6633 [110,111].

#### 2.5.4. Novel bioactive compounds from marine fungal endophytes of mangrove

Mangrove forests represent a very diverse ecosystem. They are a diverse group of about 70 species of plants that grow in salt coastal habitats. They are belonging to many botanical families, among which *Rhizophoraceae*, *Combretaceae*, *Lythraceae*, and *Avicenniaceae* are the most prevalent examples [44, 45]. Moreover, mangroves supply a distinctive and dominant ecosystem consisting of intertidal marine plants, generally trees, predominantly on tropical coastal margins around the world. It is well established that the environment in which a plant grows has a tremendous influence on the variety of metabolites produced by endophytes [4, 45].

Over 200 species of mangrove fungal endophytes were derived and characterized with structurally diverse biologically active secondary metabolites [112]. Distinctive compounds xyloketal A (**177**), B (**178**), C (**179**) and D (**180**) were gotten from the mangrove fungus *Xylaria* sp. (no. 2508) (Figure 7a). Among them compound **177** exhibited inhibiting activity against acetylcholine esterase [113]. The isolation of prostaglandin analog A (**181**) and isoflavone analog B (**182**) compounds (Figure 7a) from mangrove fungi, which appeared to be hopeful candidates for advance progress as clinically beneficial chemotherapeutic medicines from mangrove fungi for handling cancer patients were reported [114]. Eight secondary metabolites extracted from the culture of the mangrove fungal endophyte *P. chermesinum* (ZH4-E2), among them the novel azaphilones (chermesinones A-C; **183–185**), new *p*-terphenyl (3'-deoxy-6'-Odesmethylcandidusin B; **186**) with the identified *p*-terphenyl (**187**) were obtained (Figure 7a) [115]. Terphenyls compounds (**186** and **187**) showed effective inhibitory towards  $\alpha$ -glucosidase and acetyl cholinesterase. Three xanthenes sterigmatocystin (**188**), dihydrosterigmatocystin (**189**) and secosterigmatocystin (**190**) were yielded from fungal endophyte isolate 1850 derived from a leaf of *K. candel* from an estuarine mangrove in Hong Kong (Figure 7a). Sterigmatocystin (**188**) exhibited low cytotoxic activity towards tumor cell lines [116]. The antimicrobial, anticancer and antiviral activities as well as inhibitory activity against  $\alpha$ -glucosidase,  $\beta$ -glucosidase,  $\beta$ -galactosidase and tyrosinase enzymes of endophytic secondary metabolite obtained from different mangrove derived fungi were reported [4, 7]. Three compounds sporothrins A, B, and C (**191–193**) were obtained from the mangrove fungal endophyte *Sporothrix* sp. (#4335) (Figure 7a). Compound **191** showed strong inhibition activity of acetylcholine esterase [117]. Four novel guignardones F-I (**194–197**), with two identified structures guignardones A (**198**) and B (**199**) were obtained from the fungal endophyte strain A1 of the mangrove plant *S. hydrophyllacea*. These structures were tested for inhibitory activity towards MRSA (Figure 7a) [118]. Novel eremophilane sesquiterpenes (**200–202**) derived from the mangrove fungal endophyte *Xylaria* sp. BL321 with identified analog of the novel compound **203** [119]. Then it has antidiabetic activity by preventing the reducing the impact of carbohydrates in blood (Figure 7b). Three novel compounds **204**, **205** and **206** were obtained from the fungus *A. versicolor* HDN1009 (Figure 7b) [120]. Structure **204** was showed hopeful antibacterial activities towards both G-positive and

G-negative bacteria. While structures **205** and **206** showed wide cytotoxicities towards five cancer cell lines [120]. Recently, five novel anthraquinone derivatives D-H (**207–211**) with two recognized analogues (**212** and **213**) were extracted from culture of the fungus *S. casei* [121]. Compounds **207** and **209** exhibited cytotoxic activities towards 11 types of human cancer, while compounds **207**, **209**, **210**, **212** and **213** exhibited hopeful antibacterial activities. Moreover, structures **210** and **212** showed a medium anticoagulant influence but only compound **210** showed a weak antitubercular influence (Figure 7b) [121]. Moreover, three compounds **214**, **215** and **216** were gotten from fungal endophyte *Penicillium* sp. sk5GW1L derived from the leaves of the mangrove plant *Kandelia candel* (Figure 7b). Structures **214–216** displayed an effective in vitro inhibitory activity towards AChE [122]. Also, the same fungal species yielded compounds **217**, **218** and **219** (Figure 7b). Compounds **217**, **218** and **219** showed effective AChE inhibitory activity [123]. It should be emphasized that the aforementioned (**219**) previously undescribed compounds are just a few examples of endophytic products yielded by marine fungi. There are more and more endophytic compounds with different structure variety, molecules originality and biological activities waiting to be explored [124]. Particularly, reach to 51% of bioactive metabolites isolated from fungal endophytes have an unidentified chemical structure, highlighting the tremendous biotechnological prospective of this microbial cluster to discover new pharmaceuticals [124].

#### 2.6. Fungal endophytes as a source of valuable hydrolytic enzymes, biotechnological/industrial applications

Enzymes of pharmacological and medicinal importance are gaining increasing interest [125]. The fungal endophytes are an unexplored source of enzymes with different potentialities [58]. The fungal extracellular enzymes are earning significance in food industry, confectionery, textile, leather, agriculture and human health because of their high production capability with minimal cost and stabilization at different most conditions as high temperatures and pHs [126]. The fungal endophytes may yield numerous enzymes to help its host growth and protection towards pathogenesis [112]. Moreover, the fungal endophytes assault the plant tissues through yielding hydrolases as xylanase, pectinase, cellulase, lipase, laccase etc., and thus might confirm to be a potential source in finding enzymes with various potentialities [127]. Among fungal endophytes isolated from the orchid samples had the capability to yield pectinase, protease, lipase, cellulase and amylase, with highest production potential for all enzymes in *Pseudopestalotiopsis theae* [63]. The potent ability of endophytic fungi to produce important hydrolytic enzymes was previously reported. Farouk et al., assessed the capability of fungal endophytes to yield hydrolytic enzymes such as carboxymethyl cellulase, xylanase, and amylase within the host plant and all isolated endophytes genera including *Aspergillus*, *Fusarium*, *Nigrospora*, *Trichoderma*, and dark sterile mycelia were hyperactive for these industrial microbial enzymes [125]. The ability of fungi *Mucor plumbeus* and *A. terreus* to scarify sugars by their xylanolytic, cellulolytic and ligninolytic enzymes using different agro wastes, converted further into ethanol through fermentation process that can reduce the cost of producing bioethanol were reported [57].

Moreover, Thirunavukkarasu et al., proved that endophytic *Trichoderma harzianum* of the brown alga *Sargassum wightii* was the hyper active producer of xylan-degrading enzymes [128]. Thirty fungal endophytes isolated from mangrove were capable to produce different enzymatic activities including: lignin peroxidases, manganese peroxidase, laccase, endo-1,4- $\beta$ -D-glucanase and endo-xylanase [58]. Out of them *Fusarium sambucinum* and *Trichoderma camerunense* proved to be the hyper producers [128]. Shubha and Srinivas stated that out of 165 fungal endophytes, 22 various fungal species isolated from *Cymbidium aloifolium* [129]. Also, proteases providing softness to the silk fiber, used as advocate lens cleaners, healing and management of skin ulcers by removal of necrotic materials, laccases used in pulp and paper industry in addition to



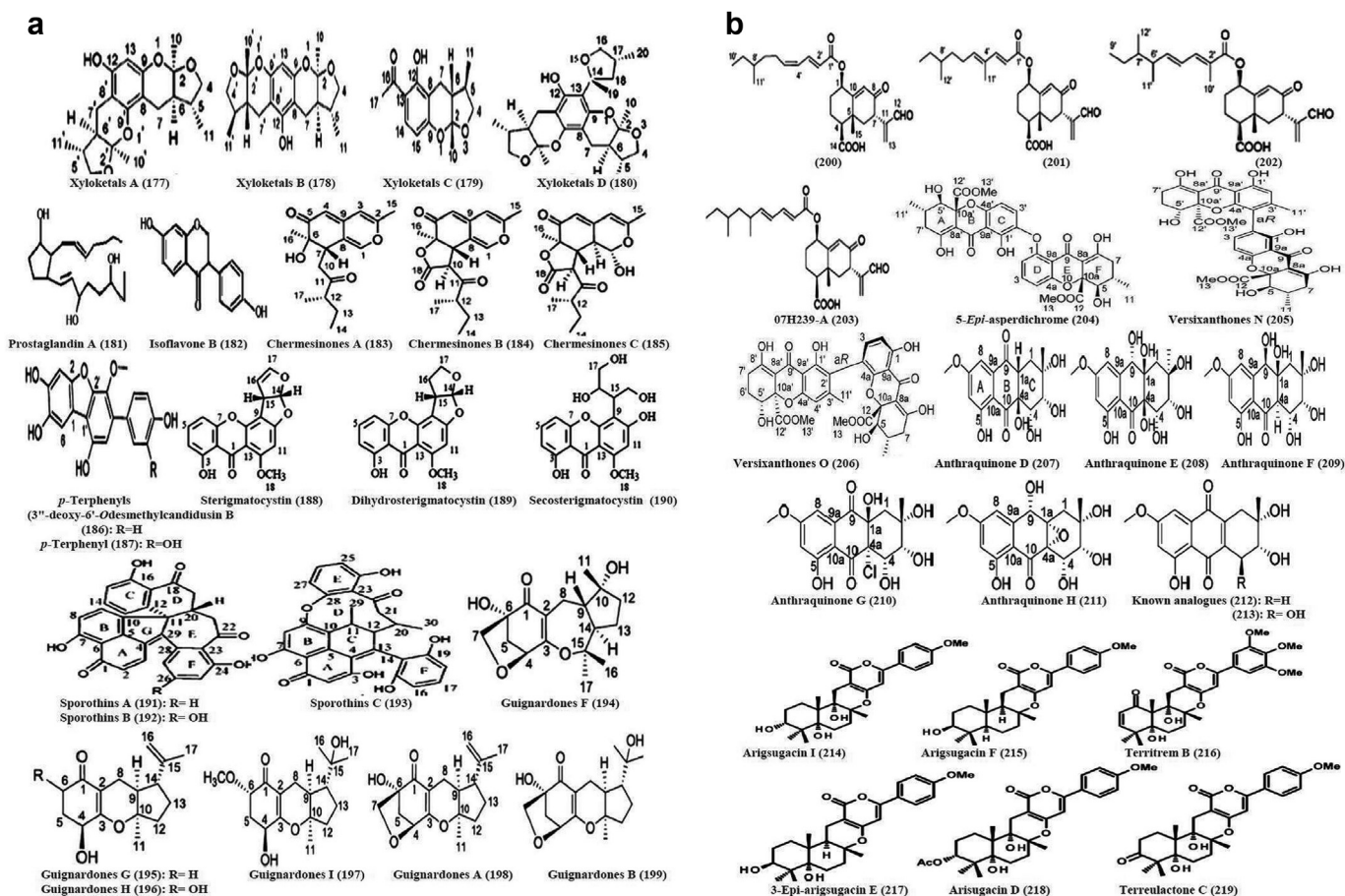


Figure 7. Secondary metabolites from marine fungal endophytes of mangrove.

bioremediation applications, keratinase with a number of medicinal and cosmetics applications as well as amylases which change starch to sugar syrup and pectinase required in food and juice industry were all detected and produced by marine endophytic fungi [25, 61, 62, 125, 130, 131, 132]. Moreover, the effective production of the antineoplastic enzymes as L-asparaginase and L-glutaminase was reported from the marine endophytic fungi [6, 7, 14, 15, 25, 64].

## 2.7. From marine fungal endophytes to anti-cancer pharmaceuticals

Currently there are more than 22,000 recognized microbial metabolites; 10% of which are microbial origin [133]. The bryostatin 1, plitidepsin, dolastatin 10, DMXBA (GTS-21), plinabulin (NPI-2358), aplidine, PM1004 (Zalypsis<sup>®</sup>), eribulin (E7389) and CDX-011 have lately entered phase II clinical test towards different cancers including colon, melanoma, pancreas, non-Hodgkin's lymphoma, Breast, lung and prostate cancer, solid human tumors, hematological malignancies, and Alzheimer's disease (Table 1) as it exerts anti-proliferative effects by targeting microtubules, proapoptotic effects; microtubules and JNK stress protein, Rac1 & JNK activation; glycoprotein NMB & microtubules; plasma membrane fluidity and/or glycoprotein NMB & microtubules. Interestingly some marine metabolites approved were approved to be used as medicines including cytarabine, ara-C, mesylate (E7389), viderabine, ara-A, ziconotide, eribulin, citarabine, omega-3-acid ethyl esters, trabectedin that belonging to nucleoside, peptide, macrolide, alkaloid, omega-3 fatty acids and polyketide targeting DNA polymerase, viral DNA, polymerase N-type, Ca channel, microtubules, inhibition of DNA synthesis, tryglyceride-synthesizing enzymes, minor groove of DNA to fight leukemia, herpes simplex, Ache, breast cancer, and liposarcoma, hypertriglyceridemia, advanced solid

tumors and carcinoma of liver, breast and lung. Other marine metabolites in advanced clinical development in phase trials I, III and VI are listed in Table 1 [133].

## 2.8. Current understanding, challenges, and future perspectives for usage of endophytic fungi

Despite the fact that endophytic mycobiology has appeared as a valuable novel arena in harnessing different industrially beneficial metabolites in different aspects of life, many features of endophytic fungi is yet to be addressed [45]. In addition, it is a group of poorly screened microorganisms that appear plentiful and dependable source of bioactive and chemically unique structures with prospective medical, agricultural, and industrial applications [68]. Also, the coevolution of marine organisms with endophytic associations was been studied extensively to increase our comprehension of their influence on physiology, biochemistry and adaptation to the changing conditions of their host [10, 124]. Specific endophytic fungal research areas must be studied in depth to comprehend the style of metabolites yielded in the host plant-endophyte niche of host and guest as well as in the host plant in reply to exciting effects of chemicals yielded by endophytes [31]. In fact, to find new biologically active metabolites, we need new fungal genera and species through extensive work to explore and study their biology and requirements to cultivate them outside their host, taxonomic work with other related fungi at structural, developmental and molecular levels followed by depositing the isolated endophytic fungi in national state or well-conserved university culture collection to extract novel effective compounds successfully. This necessitates the concerted efforts of all the microbiologists, chemists and financiers [31, 134]. Although the high diversity of endophytic fungi, most of them are obligate biotrophs and then they are unculturable and



then failed to cultivate in bioreactor for large scale production yet. Scientists can overcome this problem through extensive studies focusing on improving current strategies and designing a suitable cultivation scheme to exploit them exclusively in bioreactors outside their host in the future for producing secondary metabolites [1, 2].

### 3. Conclusions

The marine ecosystem has now been reviewed as a prolific resource for many certain niches and marine organisms that host great endophytic fungal biodiversity with potential to produce pharmaceutical and medicinal agents. Continuous exploration of sources of new medicines and marine fungal endophytes of marine macroorganisms including algae, coral, and sponge have been established to gain new dimensions to yield a range of novel bio-products with a wide range of bio-activities. It must be realized that the generation of these biologically active substances with different chemical structures by any of the marine organisms and associated fungi is an indirect or direct consequence of complex and dynamic environmental interactions in nature. Endophytic fungi can be widely exploited up to molecular/gene level to obtain sustainable and low-cost bio-resources for useful biologically active substances at large scale for various purposes. These purposes include, among others, medical field (unique anticancer, antibacterial, antioxidant, and antifungal drugs) and agriculture (to obtain high yielding crop plants or other biotechnological applications).

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#### Competing interest statement

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