MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Open Access Journal of Pharmaceutical Research
ISSN: 2574-7797

Marine Environment, the Secretive World of Endophytic Microorganisms

Elkhateeb WA* and Daba GM

Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Institute, Egypt

***Corresponding author:** Dr. Elkhateeb WA, Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries institute, National Research Centre, Dokki, Giza, 12622, Egypt; Tel: +201013241936; Fax: +20233370931; Email: waillahmed@yahoo.com

Review Article

Volume 6 Issue 2

Received Date: April 05, 2022

Published Date: June 20, 2022

DOI: 10.23880/oajpr-16000269

Abstract

Marine, endophytic microorganism creatures living in this environment should be investigated as an exceptional source for several new products and knowledge. Microorganisms obtained from such environment can be highly beneficial to science, health, and industry. Searching for novel isolates secreting potent secondary metabolites, and having promising biological activities is the target of current researches all over the world. In this review, it was highlighted that screening for endophytic fungi from marine sources with remarkable bioactivities. Many studies are required to complete investigating potentials of the promising isolated endophytic microorganisms.

Keywords: Marine; Microorganisms; Endophytes; Biological activities

Abbreviations: EtOAc: Ethyl Acetate; DKPs: Diketopiperazines; HCV: Hepatitis C Virus; ROS: Reactive Oxygen Species.

Introduction

Marine environment (Oceans and seas cover almost three quarter of the Earth's surface and host 50% -80% of life forms) represents an untapped source of fungal diversity, where it has been estimated that about 10% of fungi have been explored until now. These fungi are also becoming an appealing source of natural products. Fatal diseases require searching for new compounds with high activity and/or novel action mechanisms, screening for promising sources of biologically active compounds that fulfill the current needs of humanity is a matter of life and death. Fungi generally [1-5], and endophytic ones specifically [6-10], represent future factories and potent biotechnological tools for production of bioactive natural substances, which could extend healthy life span of humanity (as done by penicillin from centuries), and are considered promising alternatives for some high costly produced chemicals and drugs [11-15].

Endophytic mycobiota are fungi that commonly spend their life cycle (or part of it) inhabiting intercellular and/or intracellular spaces in the tissues of healthy plants, lichens, Algae, seagrass, soft coral, sponge and others marine host, without harmful aspects. Literally, the word endophyte indeed describes location of these microorganisms: 'endo' means inside and 'phyte' means plants. These endophytes have key roles in enhancing the adaptation of host plants to environmental stresses such as salinity and temperature. However, the presence of such endophytes depends on many factors including environmental factors such as, total soluble salts, pH, as well as nature and age of the host [16-20].

Various biological activities such as antitumor, antibacterial, antiviral, antimalarial, antidiabetic, hypocholesterolemic, and immunomodulatory are reported, for some metabolites secreted by endophytic fungi, such as phenols, alkaloids, isoprenoids, steroids, isocoumarines, perylene derivatives, quinones, furandiones, xanthones, terpenoids, depsipeptides, cytochalasin, polyketides, proteins, peptides, lipids, shikimates, and glycosides. Furthermore, endophytes produce various low-molecular-weight volatile organic compounds such as alcohols, ketones, esters, acids, and hydrocarbons. On the otherhand, many enzymes produced by endophytes are used nowadays in the industries of food, cosmetics, biofuels, paper, cellulose, textile, fine chemicals, detergents, biomaterials, and leather [21-25].

The present review highlights some bioactive secondary metabolites, produced by fungal endophytes isolated from marine environment, involved in medical, pharmaceutical, agricultural, and industrial applications.

Marine Endophytic Fungal Metabolites: The New World of Pharmaceutical Therapy

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 [26].

Two new sulfonyl metabolites, pensulfonoxy and pensulfonamide, together with four known metabolites were obtained from the fermentation extract of *Penicillium aculeatum*, an endophytic fungus isolated from the marine red alga *Laurencia obtusa*. The structures of the compounds were established on the basis of extensive NMR and MS spectroscopic analysis. The ethyl acetate extract exhibited potent antibacterial inhibitory activity against *Escherichia coli*, while pensulfonamide exhibited antifungal activity against *Candida albicans* with inhibition diameters of 20.5 and 18.0 mm, respectively. Moreover, pensulfonamide also displayed the most potent preferential cytotoxicity against MCF-7, while pensulfonoxy displayed relatively mild activity against HCT-116 with IC50 values of 2.18 and 5.23 μM, respectively, compared to the drug control, paclitaxel [27].

Forty-eight endophytic fungal strains were isolated and purified from ten Egyptian medicinal plants and their culture broth extracts were explored for HCV protease inhibitory activity and cytotoxicity. The ethyl acetate extracts of *Alternaria alternata* PGL-3, *Cochliobolus lunatus* PML-17, *Nigrospora sphaerica* EPS-38, followed by *Emerecilla nidulans* RPL-21 showed the most potent inhibition of HCV NS3/4A protease with IC50 17.0, 20.5, 33.6, and 54.6 μg/ml, respectively, with low cytotoxicity except for the later. The extracts of *Emericella nidulans* RSL-24, *Fusarium oxysporum* SML-41, *Emericella nidulans* RPL-21, and *Penicillium* sp. RSL-43 exhibited strong cytotoxic activity against human breast cancer cell lines (MCF-7) with IC50 10.8, 11.0, 12.5, and 13.7 μg/ ml, respectively. *Emericella nidulans* RSS-22, *Emericella nidulans* RSL-24, and *Fusarium oxysporum* SML-41 displayed a potent cytotoxic effect on human liver cancer cell lines (HEP-G2) with IC5014.8, 20.3 and 24.0 μg/ ml, respectively. Alternariol and alternariol -9-methyl ether were isolated from the ethyl acetate extract of *Alternaria alternata* PGL-3 whereas, emericellin, shamixanthone, arugosin C were isolated from the ethyl acetate extracts of *Emericella nidulans* RPL-21. The results suggest *Alternaria alternata* PGL-3 endophyte from *Punica granatum* peel as a source of antiviral lead [28].

Scale-up fermentation of the marine endophytic fungus *Penicillium chrysogenum* in biomaltpeptone media followed by cytotoxicity-guided fractionation led to the isolation of haenamindole, an unusual Diketopiperazine (DKP) alkaloid, along with other five known DKPs. Haenamindole was elucidated on the basis of comprehensive 1D and 2D NMR spectroscopic including ^{15}N-HSQC and ^{15}NHMBC and mass spectrometric analyses. The compound possesses the secondary hydroxamic acid functionality of N-piperazindione ring system confirmed by methylation in sodium dimethyl sulfate and dry dimethylformamide to yield haenamindole-22-N-methyl ether. However, haenamindole demonstrated weak HCV protease activity with an IC50 value of 76.3μM, its cytotoxicity profiling in a panel of up to 12 cell lines indicated significant cytotoxicity of the compound with pronounced selectivity for colon-38 cancer cells compared to the human normal cells [29].

Marine-derived microbes, fungi in particular, have long been recognized as a potential source of structurally novel and biologically potent metabolites [1,6]. The fungal genus *Emericella* is one of the sexual states of *Aspergillus*. Several species of this genus are saprobes, whereas others are either pathogenic or endophytic on living plants [20]. Cultivation

of this fungus in Czapek's peptone media led to the isolation of five known metabolites: sterigmatocystin, emericellin, cordycepin, ergosterol peroxide, and myristic acid from the ethyl acetate extract of the culture broth. The structures were elucidated on the basis of NMR spectroscopic analysis and mass spectrometry. The ethyl acetate extract and the isolated compounds were tested for antimicrobial properties, activity against cancer cell lines, and inhibition of the hepatitis C virus protease and possess promising anti-HCV protease activity and selective anticancer activity against liver cancer cell lines [30].

Nasr, et al. [31], studied that bioactive secondary metabolites from *Emericella nidulans* sp. Emericellin and Sterigmatocystine were isolated from the ethanolic crude extract. The chemical structure of the isolated compounds was identified by the comparison of 1D, 2D NMR and HRESIMS data with authentic spectra. Sterigmatocystin was known to have an in vitro cytotoxicity against liver cancer HEP-G2. Interestingly, the metabolic profile of n-hexane lipophilic compounds were elucidated by (GC-MS) analysis that led to the identification of phytol and farnesol (Terpenoid compounds), oliec acid, parafines and fatty acid esters. *Emericella nidulans* is a filamentous fungus which belongs to phylum Ascomycota, it was considered as a rich source of secondary metabolites with potential bioactivities. Polyketides with a benzophenone nucleus were previously isolated from the total extract of *E. nidulans* [1]. Emericellin was tested for its inhibitory activity against HCV protease using HCV NS3 protease inhibitor as a positive control. It showed a mild inhibitory effect with IC50 values of 50.0, µg/ml. Generally, Xanthonic compounds showed interesting biological activities associated with their tricyclic scaffold depending on the nature and/or position of the different substituents [6]. The relationship between activity and the presence of prenyl groups in key-positions on the xanthone nucleus was associated with some biological activities, such as inhibition of human lymphocyte proliferation, PKC modulation, antitumor, and anti-inflammatory. The structures of these metabolites were determined by MS and NMR spectral analysis [31].

Three endophytic fungal strains, *Fusarium equiseti, Scopulariopsis fusca* and *Geotrichum candidum* were isolated from the inner tissue of the brown alga *Padina pavonica*, collected from the Red Sea. The organic extracts of their liquid cultures were evaluated for their inhibition of hepatitis C virus (HCV) NS3-NS4A protease. As a result, *Fusarium equiseti* showing a high-level inhibition of HCV protease (IC50 27.0 µg/ml) was selected for further investigation on its secondary metabolites. The fungus was identified by its morphology and 18S rDNA. Bioassay-guided fractionation of the EtOAc extract of the fungus culture broth revealed seven known metabolites. The structures of these metabolites were determined by MS and NMR spectral analysis. The isolated compounds were explored for inhibition of HCV NS3-NS4A protease activity [32].

Hepatitis C virus (HCV) infection is a global problem due to the difficulties in developing a protective vaccine. Ahmed, et al. [33], demonstrated that the ethyl acetate extract of the endophytic fungus *Aspergillus versicolor* exhibited significant activity against HCV NS3/4A protease with IC50 value of 30µg/mL. The fungus was isolated from the Red Sea black sponge *Spongia officinalis* and identified by its morphology and 18S rDNA. Large-scale fermentation of the fungus followed by chromatographic purification with silica gel, Sephadex LH-20 and semipreparative HPLC of the active extract led to isolation of some known metabolites related to cyclodipeptides and the so-called diketopiperazines (DKPs). The DKP, cyclo (L-Tyr-L-Pro), displayed strong effect as HCV protease inhibitor with IC50 value of 8.2 µg/mL. A computational docking study of cyclo (L-Tyr-L-Pro) against HCV protease was used to formulate a hypothetical mechanism for the inhibitory activity of the active compound on the tested enzyme [33].

Three fungal strains, *Alternaria alternata, Eurotium chevalieri* and *Penicillium crustosum* were isolated from the normal tissues of the soft coral *Litophyton arboreum*, collected from the Egyptian Red Sea coast. The ethyl acetate (EtOAc) extracts of their liquid cultures were subjected to primary screening of anticancer and inhibition of hepatitis C virus (HCV) NS3-NS4A protease. As a result, *Alternaria alternata* showing a high-level inhibition of HCV protease (IC50 14.0 µg/mL) was selected for further investigation on its secondary metabolites. The fungus was identified by its morphology and 18S rDNA. Bioassay-guided fractionation of the EtOAc extract of *Alternaria alternata* culture broth revealed 5 metabolites: alternariol-9-methyl ether3-O-sulphate, alternariol-9-methyl ether, alternariol, maculosin and maculosin-5 [34]. The structures of these metabolites were assigned on the basis of detailed spectroscopic analysis. The biological properties of the isolated compounds were explored for inhibition of HCV NS3-NS4A protease as well as anticancer and antimicrobial activities [34].

Hepatitis C virus (HCV) NS3-NS4A protease is an attractive target for anti-HCV agents because of its important role in replication. Hawas, et al. [35], demonstrated that the ethyl acetate extract of the endophytic fungus *Penicillium chrysogenum* exhibited a potent activity against HCV NS3-NS4A protease with an IC50 value of 20 microg/ ml [35]. The fungus was isolated from the red alga *Liagora viscida* and identified by its morphology and 18S rDNA. Large-scale fermentation of the fungus in Czapek's peptone liquid medium followed by chromatographic purification of the active extract from the liquid medium allowed the isolation

of twelve known metabolites. The biological properties of the isolated compounds were explored for anti-HCV protease as well as antimicrobial and anticancer activities. A computational docking study of the active isolated compounds against HCV protease was used to formulate a hypothetical mechanism for the inhibitory activity of the active compounds on the tested enzymes [35].

The marine fungus *Aspergillus versicolor* was isolated from the inner tissue of the Red Sea green alga *Halimeda opuntia*. The fungus was identified by its morphology and 18s rDNA. Cultivation of this fungal strain led to a new metabolite named isorhodoptilometrin-1-methyl ether along with the known compounds emodin, 1-methyl emodin, evariquinone, 7-hydroxyemodin 6,8-methyl ether, siderin, arugosin C, and variculanol [36]. The structures were elucidated on the basis of NMR spectroscopic analysis and mass spectrometry. The biological properties of ethyl acetate extract and compounds 1-3 and 6-8 were explored for antimicrobial activity, anti-cancer activity and inhibition of Hepatitis C virus (HCV) protease [36].

Marine fungi and, particularly, endophytic species have been recognised as one of the most prolific sources of structurally new and diverse bioactive secondary metabolites with multiple biotechnological applications. Despite the increasing number of bioprospecting studies, very few have already evaluated the cosmeceutical potential of marine fungal compounds. Thus, many studies focused on a frequent seaweed in the Portuguese coast, *Halopteris scoparia*, to identify the endophytic marine fungi associated with this host, and assess their ability to biosynthesise secondary metabolites with antioxidative, enzymatic inhibitory (hyaluronidase, collagenase, elastase and tyrosinase), anti-inflammatory, photoprotective, and antimicrobial (*Cutibacterium acnes, Staphylococcus epidermidis* and *Malassezia furfur*) activities. Calado, et al. [37], isolated eight fungal taxa included in the Ascomycota, and in the most representative taxonomic classes in marine ecosystems (Eurotiomycetes, Sordariomycetes and Dothideomycetes). These fungi were reported for the first time in Portugal and in association with *H. scoparia*, as far as it is known. The screening analysis showed that most of these endophytic fungi were producers of compounds with relevant biological activities, though those biosynthesised by *Penicillium* sect. *Exilicaulis* and *Aspergillus chevalieri* proved to be the most promising ones for being further exploited by dermocosmetic industry. The chemical analysis of the crude extract from an isolate of *A. chevalieri* revealed the presence of two bioactive compounds, echinulin and neoechinulin A, which might explain the high antioxidant and UV photoprotective capacities exhibited by the extract. These noteworthy results emphasised the importance of screening the secondary metabolites produced by these marine endophytic fungal strains for other potential bioactivities, and the relevance of investing more efforts in understanding the ecology of halo/osmotolerant fungi [37].

Endophytes are an unexploited source of pharmacologically relevant compounds owing to their species richness and diversity. Kamat, et al. [38], reported that, a total of 26 endophytic fungi were isolated and identified from 10 marine algal samples collected from the Konkan coast, Goa, India. Eighteen of the fungal isolates belonged to phylum Ascomycota while one belonged to phylum Basidiomycota based on ITS sequencing. Further, the genus *Aspergillus* sp. was the most common and abundant endophyte found in the sampled algal species. A significant antibacterial activity against five pathogenic bacteria was exhibited by the extracts of fungal isolates AG1.1, AG1.1 (G) and VG2.6 (agar diffusion assay). The extracts of fungal endophytes VB1.1, PG1.2 and VG2.6 demonstrated good antioxidant activity (DPPH scavenging assay). Further, cytotoxicity of all the endophytic extracts on human cancer cell lines was determined by MTT and resazurin assay. The crude extract of *Aspergillus unguis* (AG 1.2) showed the highest cytotoxic potential on cervical cancer (HeLa), breast cancer (MCF-7), lung cancer (A549), and skin cancer (A431) cell lines in a concentration dependent manner. Moreover, Gas Chromatography-Mass Spectroscopy analysis of the extract of A. unguis (AG 1.2) confirmed the presence of several bioactive metabolites including azelaic acid, azetidine, and furopyrans. The extract of *A. unguis* (AG 1.2) demonstrated G1 phase cell cycle arrest, reactive oxygen species (ROS)-dependent MMP loss and apoptosis-dependent cell death in A431 cells. The algae-derived fungal endophytes of Konkan coast are a rich source of novel pharmaceutically active compounds as indicated by Kamat, et al. [38].

Zhou, et al. [39], studied and measured the antibacterial and antitumor cell activity for secondary metabolites of marine fungi, which were isolated from different habitats in coastal regions. 195 strains of marine fungi were isolated and purified from three different habitats. They biologically active experiment results showed that fungi isolation from the mangrove habitats had stronger antibacterial activity than others, and the stains isolated from the estuarial habitats had the least antibacterial activity. However, the strains separated from beach habitats strongly inhibited tumor cell proliferation in vitro, and fungi of mangrove forest habitats had the weakest activity of inhibiting tumor. Meanwhile, 195 fungal strains belonged to 46 families, 84 genera, and 142 species and also showed 137 different types of activity combinations by analyzing the inhibitory activity of the metabolites fungi for 4 strains of pathogenic bacteria and B-16 cells [39].

Different studies investigated the biological activity of marine fungi isolated from different habitats and the results help us to understand bioactive metabolites of marine fungi from different habitats, and how to selected biological activity fungi from various marine habitats effectively [40-42].

Marine fungi are rich in antimicrobial compounds such as anthrones, cephalosporins, peptides, steroids [43]. These compounds which are derived mainly focused in the area of anti-inflammatory, anti-oxidant, anti-fungal, anti-microbial, anti-fouling activity. Bioactive terpene compounds are produced by marine fungi and marine derived fungi can produce sclerotides, trichoderins. Marine fungi have become the richest sources of biologically active metabolites and structurally novel in the marine environment. In a recent study the marine derived fungi *dichotomomyces cejpii* exhibits activity towards cannabinoid which is used to treat alzheimer dementia. *Aspergillus unguis* showed significant acetyl cholinesterase besides its anti-oxidant activity. These acts as a promising intent for discovery of pharmaceutically important metabolites like alkaloids, peptides. Computational (in silico) strategies have been developed and broadly applied to pharmacology advancement and testing [43,44].

In recent years, a considerable number of structurally unique metabolites with biological and pharmacological activities have been isolated from the marine-derived fungi, such as polyketides, alkaloids, peptides, lactones, terpenoids and steroids. Some of these compounds have anticancer, antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, antibiotic and cytotoxic properties. According to a classical definition, marine fungi are divided into obligate marine fungi and facultative marine fungi [45].

In fact, marine fungi often live as symbionts in algae, mangrove, coral, sea anemone, starfish, sea urchin, seagrass, and, especially, sponges. Collection of marine fungi usually requires the collection of the host or supporting material (e.g., algae, marine invertebrates, sediment or water, and even driftwood). Herein, a neutral term "marine-derived fungi" was used, which includes any fungal strain obtained from marine environment using cultivation techniques with "marine" media [46,47].

Marine fungi recently appeared as producers of an amazing variety of structurally unique secondary metabolites, they may represent a promising resource for identifying new candidates for therapeutic drugs or daily additives. Anthraquinones and their derivatives constitute a large group of quinoid compounds with about 700 molecules described. They are widespread in fungi and their chemical diversity and biological activities recently attracted attention of industries in such fields as pharmaceuticals, clothes dyeing, and food colorants [48].

Conclusion

Emergence of new lethal diseases require continuous screening for new microorganisms that possibly produce novel compounds capable of treating such diseases through supporting the action of currently available drugs and/or substitute them. The marine environment is the most essential sources regarding to natural products in research, since organisms from oceans have exhibited exceptional biological, biochemical, and biosynthetic potential. Similarly, microorganisms' natural products represent a substantial area for novel therapeutic compounds search. Many reviews highlighted microbial metabolites as targets for discovery and development of new drugs, especially anticancer, antibiotics, antifungals, and antiparasitics and others. Marine fungal endophytes are therefore virtually unlimited sources of novel compounds with numerous potential therapeutic applications due to their immense diversity and proven ability to produce natural products of medicinal and pharmaceutical importance, thus inspiring researchers to further study them. This review represents some of the endophytic fungi isolated from marine sources that produce metabolites with various biological activities. The potential for the exploitation in the pharmaceutical activities and concerns are also discussed. The marine environment have unique content of living microorganisms attract and encourage for searching inside these remarkable places for new species that may contribute in saving health of humanity.

References

1. Elkhateeb WA, Daba GM (2018) Where to Find? A Report for Some Terrestrial Fungal Isolates, and Selected Applications Using Fungal Secondary Metabolites. Biomed J Sci & Tech Res 4(4): 4000-4003.

2. Elkhateeb WA, Daba GM (2019) The amazing potential of fungi in human life. ARC J Pharma Sci AJPS 5(3): 12-16.

3. Elkhateeb WA, Daba GM (2019) Epicoccum species as potent factories for the production of compounds of industrial, medical, and biological control applications. Biomed J Sci & Tech Res 14(3): 10616-10620.

4. Elkhateeb WA, Daba GM (2019) Myrothecium as promising model for biotechnological applications, potentials and challenges. Biomed J Sci & Tech Res 16(3): 12126-12131.

5. Daba GM, Mostafa FA, Elkhateeb WA (2021) The ancient koji mold (Aspergillus oryzae) as a modern biotechnological tool. Bioresour Bioprocess 8(1): 1-17.

6. Daba GM, Elkhateeb WA, Thomas PW (2018) This era

of biotechnological tools: an insight into endophytic mycobiota. Egyptian Pharmaceu J 17(3): 121-128.

7. Elkhateeb WA, EL-Ghwas DE, AL Kolaibe AG, Akram M, Daba GM (2021) Yeast the Present and Future Cell Facture. J Mycol Mycological Sci 4(2): 000142.

8. Elkhateeb WA, Elnahas MO, Daba GM, Zohri AN (2021) Biotechnology and Environmental applications of Trichoderma spp. Research Journal of Pharmacognosy and Phytochemistry 13(3): 149-157.

9. Elkhateeb WA, Kolaibe AG, Daba GM (2021) Cochliobolus, Drechslera, Bipolaris, Curvularia different nomenclature for one potent fungus. Journal of Pharmaceutics and Pharmacology Research 4(1): 1-6.

10. Elkhateeb WA, Kolaibe AG, Elnahas MO, Daba GM (2021) Highlights on Chaetomium morphology, secondary metabolites and biological activates. Journal of Pharmaceutics and Pharmacology Research 4(1): 1-5.

11. Elkhateeb WA (2005) Some mycological, phytopathological and physiological studies on mycobiota of selected newly reclaimed soils in Assiut Governorate, Egypt, pp: 238.

12. Elkhateeb WA, Zohri AA, Mazen M, Hashem M, Daba GM (2016) Investigation of diversity of endophytic, phylloplane and phyllosphere mycobiota isolated from different cultivated plants in new reclaimed soil, Upper Egypt with potential biological applications. Inter J MediPharm Res 2(1): 23-31.

13. Elkhateeb WA, Daba GM (2022) Insight into secondary metabolites of Stachybotrys, Memnoniella, Doratomyces and Graphium between benefits and harmful. Biotechnology and Bioprocessing 3(1): 1-6.

14. Elkhateeb WA, Daba GM (2021) The endophytic fungi Pestalotiopsis what's for it and what's on it? Journal of Pharmaceutics and Pharmacology Research 4(1): 1-5.

15. Elkhateeb WA, Daba GM (2021) Stemphylium and Ulocladium between Benefit and Harmful. J Biomed Res Environ Sci 2(11): 1117-1120.

16. Elkhateeb WA, Daba GM (2022) Chemical and Bioactive Metabolites of Humicola and Nigrospora Secondary Metabolites. Journal of Pharmaceutics and Pharmacology Research 5(1): 1-4.

17. Elkhateeb WA, Mousa KM, ELnahas MO, Daba GM (2021) Fungi against insects and contrariwise as biological control models. Egyptian Journal of Biological Pest Control 31(13): 1-9.

18. Elnahas MO, Elkhateeb WA, Daba GM (2020) All in one Thermoascus aurantiacus and its Industrial Applications. International Journal of Pharma Research and Health Sciences 8(6): 3237-3241.

19. Elkhateeb W, Akram M, Zohri A, Daba G (2022) Fungal Enzymatic Cocktails Benefits and Applications. Pharm Res 6(1): 000258.

20. Elkhateeb WA, Daba GM (2020) The Exceptional Endophytic Fungi, Emericella (Berk.) and Phoma (Sacc.) Genera. International Journal of Research in Pharmacy and Biosciences 7(1): 1-6.

21. Elkhateeb WA, Elnahas MO, Daba GM (2021) Bioactive metabolites of Cunninghamella, Biodiversity to Biotechnology. Journal of Pharmaceutics and Pharmacology Research 4(3): 1-5.

22. Elkhateeb WA, Daba GM (2022) Botryotrichum and Scopulariopsis Secondary Metabolites and Biological Activities. J Biotechnology and Bioprocessing 3(1): 1-4.

23. Elkhateeb WA, Daba GM, Elnahas MO, Thomas PW (2019) The rarely isolated fungi: Arthrinium sacchari, Beltrania querna, and Papulaspora immersa, potentials and expectations. ARC Journal of Pharmaceutical Sciences 5(4): 10-15.

24. Elkhateeb WA, Kolaibe A, Elkhateeb A, Daba GM (2021) Allergen, pathogen, or biotechnological tool? The dematiaceous fungi Alternaria what's for it and what's on it? J Pharmaceutics and Pharmacology Research 4(3): 1-6.

25. Elkhateeb WA, Daba GM (2022) Insight into Secondary Metabolites of Circinella, Mucor and Rhizopus the Three Musketeers of Order Mucorales. Biomed J Sci & Tech Res 41(2): 32534-32540.

26. El Bondkly EA, El Bondkly AA, El Bondkly AA (2021) Marine endophytic fungal metabolites: A whole new world of pharmaceutical therapy exploration. Heliyon 7(3): e06362.

27. Hawas UW, El Kassem LTA, Ahmed EF, Alghamdi RA (2021) Bioactive sulfonyl metabolites from the Red Sea endophytic fungus Penicillium aculeatum. Natural Product Research 36(11): 2713-2721.

28. El Kassem LA, Hawas UW, El Souda S, Ahmed EF, El Khateeb W, et al. (2019) Anti-HCV protease potential of endophytic fungi and cytotoxic activity. Biocatalysis and Agricultural Biotechnology 19: 101170.

29. Hawas UW, El Kassem LTA (2019) Anticancer and antiviral diketopiperazine produced by the Red Sea

endophytic fungus Penicillium chrysogenum. Letters in Organic Chemistry 16(5): 409-414.

30. Hawas UW, El Kassem LT, Ahmed EF, Emam M (2012) In-vitro bioassays on the metabolites of the fungus Emericella nidulans isolated from the Egyptian Red Sea algae. Egyptian Pharmaceutical Journal 11(2): 124-128.

31. Nasr HM, Hawas UW, Mousa SA, Alasmaey M, Ahmed EF (2018) Isolation and identification of Emericella nidulans secondary metabolites. Chemistry Research Journal 3(2): 114-119.

32. Hawas UW, Al Farawati R (2017) Chemical constituents and antiviral activity from marine endophytic fungi from Red Sea alga Padina pavonica. J Chem Soc Pak 39(3): 478-483.

33. Ahmed EF, Rateb ME, El Kassem A, Hawas UW (2017) Anti-HCV protease of diketopiperazines produced by the Red Sea sponge-associated fungus Aspergillus versicolor. Applied biochemistry and microbiology 53(1): 101-106.

34. Hawas UW, El Desouky S, El Kassem A, Elkhateeb W (2015) Alternariol derivatives from Alternaria alternata, an endophytic fungus residing in red sea soft coral, inhibit HCV NS3/4A protease. Applied biochemistry and microbiology 51(5): 579-584.

35. Hawas UW, El Halawany AM, Ahmed EF (2013) Hepatitis C virus NS3-NS4A protease inhibitors from the endophytic Penicillium chrysogenum isolated from the red alga Liagora viscida. Z Naturforsch C J Biosci 68(9-10): 355-366.

36. Hawas UW, El Beih AA, El Halawany AM (2012) Bioactive anthraquinones from endophytic fungus Aspergillus versicolor isolated from red sea algae. Arch Pharm Res 35(10): 1749-1756.

37. Calado MD, Silva J, Alves C, Susano P, Santos D, et al. (2021) Marine endophytic fungi associated with Halopteris scoparia (Linnaeus) Sauvageau as producers of bioactive secondary metabolites with potential dermocosmetic application. PloS one 16(5): e0250954.

38. Kamat S, Kumari M, Taritla S, Jayabaskaran C (2020) Endophytic fungi of marine alga from Konkan Coast, India—a rich source of bioactive material. Front Mar Sci 7: 31.

39. Zhou S, Wang M, Feng Q, Lin Y, Zhao H (2016) A study on biological activity of marine fungi from different habitats in coastal regions. Springer Plus 5(1): 1-8.

40. Jeewon R, Luckhun A, Bhoyroo V, Sadeer N, Mahomoodally M, et al. (2019) Pharmaceutical potential of marine fungal endophytes. Endophytes and Secondary Metabolites pp: 1-23.

41. Zhang P, Li X, Wang BG (2016) Secondary metabolites from the marine algal-derived endophytic fungi: Chemical diversity and biological activity. Planta Med 82(9-10): 832-842.

42. Sarasan M, Puthumana J, Job N, Han, J, Lee J, et al. (2017) Marine algicolous endophytic fungi-a promising drug resource of the era. J Microbiol Biotechnol 27(6): 1039-1052.

43. Devi PB, Jayaseelan R (2020) Natural Medicinal Compounds from Marine Fungi towards Drug Discovery: A Review. Drug Design-Novel Advances in the Omics Field and Applications.

44. Kjer J, Debbab A, Aly AH, Proksch P (2010) Methods for isolation of marine-derived endophytic fungi and their bioactive secondary products. Nat Protoc 5(3): 479-490.

45. Kohlmeyer J, Kohlmeyer E (1979) Marine Mycology: The Higher Fungi. Academic Press: New York, NY, USA, pp: 704-705.

46. Jin L, Quan C, Hou X, Fan S (2016) Potential pharmacological resources: Natural bioactive compounds from marine-derived fungi. Mar Drugs 14(4): 76.

47. Handayani D, Artasasta M, Safirna N, Ayuni D, Tallei TE, et al. (2020) Fungal isolates from marine sponge Chelonaplysilla sp.: Diversity, antimicrobial and cytotoxic activities. Biodiversitas Journal of Biological Diversity 21(5): 1954-1960.

48. Fouillaud M, Venkatachalam M, Girard Valenciennes E, Caro Y, Dufossé L (2016) Anthraquinones and derivatives from marine-derived fungi: Structural diversity and selected biological activities. Mar drugs 14(4): 64.