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Marine Marvels: Exploring the Antifungal Potential of Seaweed-derived Compounds

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Macroalgae, Antifungal compounds, Phaeophyceae, Rhodophyceae, Chlorophyta, Extraction.

ABSTRACT:

Marine macroalgae are commonly known as seaweeds. They have been traditionally used as an edible food source enriched with nutrients such as vitamins, minerals, and fibers and low calories. Seaweeds produce bioactive substances like alkaloids, polysaccharides, polyenes, polyunsaturated fatty acids (PUFA), peptides, and proteins. The inappropriate use of antifungal medications to treat fungi infections has led to increasing resistance in the fungi that are being treated. Currently, there are only a few antifungal medicines available for use in therapy for fungal infections. In recent times most researchers have been interested in formulating newer antifungal compounds from natural ecosystems. The antifungal compounds exhibited by marine macroalgae and extraction methods of biologically active compounds from marine seaweeds are discussed in this review. The data included in this article are extracted from Google Scholar, PubMed, and NCBI from the years 2010 to 2023 by using keywords such as Marine macroalgae, antifungal compounds, seaweed, and extraction methods.

1. Introduction

Earth being surrounded 70% by seawater, has a marine ecosystem which is the home of various diverse species like algae, sponges' chitosan to name a few. These marine living organisms produce several bio-active compounds have been found and commercially utilized. [1,2] Kingdom plantae includes Algae, that comprises of two major groups, microalgae and microalgae. Macroalgae have been traditionally used for nutritional and medicinal properties. Seaweed or marine macroalgae can produce metabolites that exhibit various biological activities.[4,5,6] The most common classification of macroalgae is Chlorophyceae (green), Rhodophyceae (red), and Phaeophyceae (brown) based on their pigmentation. Macroalgae produce bioactive substances like alkaloids, polysaccharides, polyenes, polyunsaturated fatty acids (PUFA), peptides, and proteins. [8,9] multi-drug resistant organisms are resistant to most synthetic antibiotics. To address this issue, developing novel, effective and alternative drugs are crucial. Ulva Lactuca, the edible green algae has been described for the antimicrobial activity of its acrylic acid content way back in 2008. [10] This article reviews the macroalgae exhibiting antifungal effects of marine macroalgae and extraction methods of biologically active compounds.

2. Methods

This methodical comprehensive review was conducted across various scientific databases including PubMed, Scopus, and Google Scholar employing keywords like Marine macroalgae, antifungal compounds, seaweed, and extraction methods. Research studies published from 2000 and 2023 were included in this review.

3. Antifungal compounds from brown algae:

Brown algae are mostly distributed in the marine environment with less than 1% being found in freshwater. The Phaeophyceae are called brown algae as they contain a brown-coloured pigments which is carotenoid in nature and fucoxanthin. In addition, some species, produce various Phaeophyceae tannins.[11] The brown algae have diverse nutritional values and medicinal values. In recent days the compounds present in the macroalgae shows an increase in their antimicrobial and bioactive activity, this leads to the development of novel antibiotics with comparably

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fewer side effects and are more cost-effective than the synthetic drug The study shows *Padina gymnospora* (brown algae) extract strongly inhibits the *Cryptococcus neoformans* with a MIC value of 23.00±1.78 and Turbinaria conoides acetone extract produces a mild inhibitory effect against *Aspergillus niger* with a MIC value of 3.00±0.89.[12] Purified phlorotannins were extracted from algae Fucus spiralis, Cystoseira nodicaulis, and Cystseira usneoides, the ergosterol contained in yeast and dermatophytes were effectively reduced by this extract, respectively. Phlorotannin's extract purified from F. spiralis decreases the amount of chitin present in cell wall of *Candida albicans*, Epidermophyton floccosum, and *Trichophyton rubrum*.[13] Several bio-active compounds obtained from Phaeophycea also known as brown algae led to developments in the synthesis of novel therapeutic drugs and food supplements. The lipid present in brown seaweeds like Sargassum horneri and Saccharina japonica, was purified with acetone-methanol mix extraction and on testing showed antifungal action against the yeast *Candida albicans* and mold *Aspergillus brasiliensis*.[14] Lobophorolide is an antifungal compound isolated from Lobophora variegate. Lobophorolide shows inhibitory action against Amphotericin-resistant *Candida albicans*.[15] The Metaterpenoid methoxybifurcarenone 138 is a compound that has both anti-bacterial and anti-fungal activity, that was purified from Cystoseira tamariscifolia.[36] Pressurized liquid extracted from Himanthalia elongate had an antifungal effect on Aspergillus niger and C. albicans.[16]

4. Antifungal compounds from red algae:

Rhodophyceae is also known as red algae because of their phycobilin pigments. Rhodophyceae is the largest class of algae containing bioactive compounds which are applied in biotechnology industries and various food supplement formulae. Numerous significant bioactive compounds have been reported in red algae. [17] The *Microsporum canis* and *Trichophyton verrucosum* rate of colonies development are reduced by *Dilsea carnosa* (commonly referred to as sea belt), *Laurencia pinnatifida* , *Polysiphonia lanosa* , and *Odonthalia dentata* extraction with alteration in levels of inhibitory activity.[18] *Rhodomela confervoides* (red algae) have the highest inhibiting effect against *Candida albicans* and *Mucor ramaniannus*, this was evaluated by the disc diffusion method.[19] *Laurencia dendroidea* (red algae) extract effectively resists the *Candida lagenarium* growth and compounds were identified as terpenes neophytadiene, ester ethyl hexadecanoate, obtusol elatol; and cartilagineol.[20] The Methyl4-{(2,5-dibromo-3,4-dihydroxidebenzyne)[2,3,6-tribrom-4,5-dihydoxybenzyl)carbamoyl] amino} butanoate is a compound purified from *Symphyocladia latiuscula* for antifungal effect against *Candida albicans* and its Minimum inhibitory concerntation value is 37.5microgram per milli liter.[21] Venkataraghavan Raghunathan et al, 2019 reported that Eicosanoic acid purified from *Gracilaria corticate* has an inhibitory effect against *Candida albicans and Candida dubliniensis.*[22] An oleic acid compound isolated from *Gracilaria corticate* was also effective against *Candida albicans* and *Aspergillus spp*.[23] The Bromo phenol,2,3,6-tri bromo -4,5-dihydroxy benzoyl methylsulphoxide has been purified from *Symphyocladia latiusculathat* and shows antifungal spectrum against *Candida albicans.*[24] Lane.et.al., reported that callophycoic acids and bromoplides were extracted from(Fijian red alga) *Callophycus serratus* and these compounds inhibits the growth of marine pathogen *L.thalassiae.* Cholestane and aldehyde derivative compounds extracted from *Laurencia papillosa* show an inhibitory effect on *Candida albicans, and Aspergillus. fumigatus and A. flavus.*[25] Julio Cesar Fernandes et.al. 2012 reported that the terpenes Neophytadiene(C20H38),cartilagineol (C15H23Br2ClO), and ester ethyl palmitate were purified from *Laurencia dendroidea* inhibit the growth of *Candida lagenarium.* [26].

5. Antifungal activity of green algae:

Green macroalgae are in the phylum Chlorophyta. Pigments in Chlorophyta are carotene, xanthophylls, and chlorophylls a and b. In recent days *U.intestinalis, U.lactuca, and Codium sp.* extracts were commercialized.[27] Caulerprenylols A (1) and B (2) are the two novel prenylated para-xylene compounds that are purified from the green algae *Caulerpa racemose*. These compounds have been shown a broad antifungal spectrum against yeast *Candida glabrata*, Dermatophytes *Trichophyton rubrum*, and yeast-like fungi *Cryptococcus neoformans* in in-vitro bioassay. When compared with commercially available amphotericin B, caulerprenylols A and B show effective

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activity.[28] Among tropical green algae *Penicillus capitatus* contains Capisterones A, Capisterones B and triterpene sulfate esters compounds. The capisterones exhibit inhibitory activity against the *Lindra thallasiae*, an aquatic pathogen of various sea grasses.[29] *Cladophoropsissp., Tydemaniasp., and Ulva prolifera* are the species of green algae. These algal extracts were purified and introduced against asthmatic fungal pathogens. Among these, the algal extracts of *Ulva prolifera* have shown effective antifungal activity.[30] Walters D et al. 2004 have reported that the Linoleic acids extracted from *Ulva fasciata* reduced the mycelial growth of *R. solani and C. perniciosa.* Acetone extract of *Enteromorpha intestinalis* reduces the development of filamentous fungus *Aspergillus flavus, Aspergillus. fumigatus,* and yeast *Candida albicans. Ulva Lactuca*, green algae have vast commercial applications, the Methanolic extract of *Ulva Lactuca* has an inhibitory effect against *Mucor ramaniannus* and *Candida albicans.*

Algal extract	**Antifungal Compounds**	**Organism**	**Reference**
Symphyocladia latiuscula	Methyl4-{(2,5-dibromo-3,4-dihydroxidebenzyne)[2,3,6-tribrom-4,5-dihydoxybenzylcarbamoyl] amino} butanoate	*Candida albicans*	Xiuili Xu et.al,2014
Symphyocladia latiuscula	2,5-dibromo-3,4-dihydroxy-6-(2,3,6-tribro-mo-4,5-dihydroxybenzyl) benzyl methyl ether	*Candida albicans*	Xiuili Xu et.al,2014
Gracilaria corticata	Eicosanoic acid	*Candida albicans and Candida dublinien sis*	Venkataragha van ragunathn et.al,2019
Gracilaria corticata	Oleic acid	*Candida albicans and Aspergilll us spp.,*	Liu et.al,2017
Lobophora variegata	Lobophorolide	Amphote ricin-resistant-strain *Candida albicans*	Ebaa M. EI-Hossary et.al.,2016
Symphyocladia latiuscula	Bromophenol,2,3,6-tribromoo-4,5-dihydroxybenzylmethyl sulphoxide	*C.albican s*	Xu et. al,2012
Penicillius capitatus	Capisterones A and B	*Linder thallasiae*	Ebaa M. EI-Hossary et.al.,2016
Fucus spiralis	Phlorotannins	*C.albican s,Epider mophyton floccosu m and Trichoph yton rubrum*	Lopes et.al,2013
Cystoseira nodicaulis	Phlorotannins	*C.albican s*	Lopes et.al,2013
Caulerpa racemosa	Caulerprenylols A and B	*Candida glabrata, Cryptoco ccus neoforma ns and Trichoph yton rubrum*	Liu et.al,2013
Gambierdiscus toxicus	Gambieric acids A and B	*Aspergill us.niger*	Sato and Sasaki 2005
Callophycus serratus	Callophycoic acids And bromophycolides	*Lindra thalassia e*	Lane et al.2009
Ulva fasciata	Linoleic acids	reduced mycelial growth of *R. solani and C. pernicios a*	Walters D et al.,2004

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Laurencia papillosa	Cholestane derivative 3α,6α-dihydroxy-5beta-cholestan-12-one and aldehyde derivative (E)-2-{(E) tridec-2-en-2-yl} heptadec-2-enal	*C. albicans, A. fumigatus, and A. flavus.*	Alarif et.al.2011
Saccharina japonica and Sargassum horneri	Oil contents purified with acetone-methanol mix extraction.	*C. Albicans and Aspergillus brasiliensis*	Saravana periaswamy et.al.,2015
Rhodomela confervoides	Methanolic extract	*Candida albicans and Mucor ramanianus*	K Saidani et al.,2012
Laurencia dendroidea	The terpenes neophytadiene, cartilagineol, obtusol elatol; and the ester ethyl hexadecanoate	*Candida lagenarium*	Julio Cesar fernandes et.al., 2012
Enteromorpha intestinalis	Acetone extract	*A. flavus, A. fumigatus and C. albicans*	Kosanic et.al., 2015
Himanthalia elongata	Pressurized liquid extract	*Aspergillus niger and C. albicans*	Plaza et.al., 2010
Cystoseira tamariscifolia	Metaterpenoid methoxybifurcarenone	*Botrytis cinerea, Fusarium oxysporum,* and *verticilliium alboatrum.*	Hakim and patel et.al, 2020

Table 1: Antifungal compounds from different marine macroalgae

6. Anti-fungal compounds extraction techniques from marine macroalgae:

In the purification of antifungal compounds from the macroalgae, it is necessary to identify and employ a specific method for compound extraction. Supercritical fluid extraction, Ultrasound assisted extraction, and Micro-wave assisted extraction are the usual methods for purification of biologically active compounds from natural source.

6.1 Super-critical Fluid Extraction (SFE):

Super-critical fluid extraction is a method of separating a specific component from the mixture of extracts by using supercritical fluids as solvent. Predominantly CO2 is a super-critical fluid because of its non-toxic, odorless, tasteless, and cost-effective and its high diffusion coefficient. Carbon dioxide can be sometimes altered with cosolvents like methanol nor ethanol. Since CO2 is non-polar solvent only the nonpolar compounds can be extracted in this extraction method.[31] Due to the low velocity of supercritical fluids, there is an effective extraction of a specific component and high yield. The operating temperature is at 40-80 ℃ and 25-40 MPa Pressure. SFE-CO_2 is used in food, pharmaceuticals, and nutritional Industry applications due to its non-toxic properties and can be easily removed from the product. Phenolic compounds and carotenoids are mostly isolated from marine macroalgae reported by SFE- CO_2 extraction. The brown algae *Saccharina japonica* and *Sargassum horneri* were extracted by the SC-CO2 method, it has antioxidant, antimicrobial, and antihypertensive active compounds.[14] These extracts showed potential anti-bacterial activity against *Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes, Escherichia coli,* and antifungal spectrum against *Candida albicans,* and *Aspergillus brasiliensis.*

6.2 Ultra Sound Assisted Extraction (UAE):

In Ultrasound assisted extraction (UAE) the separation of components can be done by use of ultrasound waves ranges greater than 20 kHz upto100 kHz. The ultrasound-assisted extraction produced ultrasound waves which created bubbles and cavitation.[32] These bubbles cause pores in the cell membrane; this occurrence is known as sonoporation. The opening up of the biological matrix leads to an increase in bioactive

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compounds. Based on the path, the ultrasound wave distracts the sample the operating conditions are of two types indirect sonification (ultrasonic bath) and direct sonification (ultrasonic probe). The different solvents used in UAE are ethanol, distilled water, and methanol. The study shows that biological compounds purified from algae by UAE is the most feasible extraction method for the purification of biological compounds.[33]

6.3 Microwave-Assisted Extraction (MAE)**:**

The MAE method uses microwave energy to heat the solvent-sample mixture and to partition analytes from the sample matrix into the solvent. When applying the non-ionizing electromagnetic wave frequency ranging from 300 MHz- 300 GHz to the sample matrix the structure of the cell disrupts. MAE is an automated technique for extraction that has multiple advantages such as there is the possibility that multiple samples can be extracted simultaneously and it able to rapidly heat the mixture of sample-solvent.[34] Because of its low solvent conception, rapid extraction, and high extraction efficiency, the MAE is widely used for pharmaceutical analysis, food inspection, environmental detection, and agricultural sample analysis, as a sample preparation technique.[35] The parameters for Microwave-assisted extraction are sample size, the volume of solvent to extract, temperature to be maintained, duration of extraction, and frequency of the microwave should be standardized for efficient extraction.

Conclusion:

Among different marine sources, macroalgae biomass has been appraised as an easily available source for a broad range of biologically active substances. Marine macroalgae have a promising role in the production of novel antimicrobial compounds and they have been widely utilized in biotechnology and pharmacology industries. Moreover, compounds having antifungal properties extracted from algae can be subjected to extensive in vivo studies for the development of effective antifungal drugs.

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