Algal bioactive diversities against pathogenic microbes

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Algae are described as heterogeneous group of organisms with considerable metabolic diversities. Currently, various bioactive compounds are discovered, isolated and used from different classes of algae to develop novel pharmaceuticals. Detectable substances such as, sterols and stanols, isoprenoide, terpenoids, steroid, phenolic compounds, fatty acids, acrylic acid and alkaloids in their extracts provide different types of algae considerable mode of biological action. As a matter of fact, these bioactive diversities plus their rapid growing rate turned algae to be exceptional sources to obtain antimicrobials, anticancer, antioxidants, antiviral, anti inflammatory, *wound healing and* neuroprotective compounds.

Keyword Algae, antimicrobial compounds, pathogenic microbes.

1. Introduction

The term “antibiotic” describes any compound that kills or inhibits the growth of microorganisms. Antibiotics are produced naturally or chemically based on isolated natural products, support to this, of the twelve antibacterial classes, nine are derived from natural product [1]. Marine ecosystem includes a nonstop resource of immense organic compounds with vast biological activities which it raises a great interest among natural products researches. Algae are eukaryote photosynthetic organisms with polyphyletic and paraphyletic characteristics ranging from unicellular to multicellular. Based on scientific classification algae can be organized in 6 phyla: Chrysophyta (diatoms), Chlorophyta (green algae), Euglenophyta (euglenoids), Phaeophyta (brown algae), Pyrrophyta (dinoflagellates) and Rhodophyta (red algae). By using DNA sequence technique algae are classified in ten major phyla including *Heterokontophyta, Glaucophyta, Euglenophyta, Cryptophyta, Haptophyta, Rhodophyta, Dinophyta, Chlorophyta* (green algae) and the prokaryotic *Cyanophyta* and *Prochlorophyta* [2,3]. Each class of algae known to produce a broad range of secondary metabolites with different biological mode of action but just a small subset of these compounds have been discovered, screened and isolated. Algal rapid growing rate plus their diverse range of secondary metabolites present them as potentially prolific sources for production of highly bioactive metabolites. Diversities of algae are currently being used for productions of food, pharmaceuticals, cosmetics, fertilizers, and biofuels [4, 5, 6].

Algae maintain wide distributions ranging from sea to wastewater; some of them like unicellular diatoms are 3–10 µm length and the others like multicellular giant kelps grow up to 65 meters in length. Evidences indicate that, algae contain useful substances including pigments (*β* carotene, astaxanthin, zeaxanthin, lutein, canthaxanthin, chlorophyll, phycoerythrin, fucoxanthin and phycocyanin), *polyunsaturated fatty acids* (docosahexaenoic acid, eicosapentaenoic acid, arachidonic acid), antioxidants (catalases, polyphenols, superoxide, dismutase, tocopherols), vitamins (A, B_{12}, C, D, E, K), essential amino acids (Leucine, Aspartic acid, Glutamic acid, Phenylalanine, Asparagine, Glycine) and antimicrobials (tropodithietic acid, labdane diterpenes, brominated hydroquinones, phlorotannins). Most of the existed chemical elements in Algae such as, sulfur, magnesium, phosphor, potassium or iron are necessary and active factors in the structure of vitamins or special enzymes incorporated in the human body [7, 8, 9]. In this regard multicellular, macroscopic, benthic marine algae like seaweeds are rich in B vitamins and also contain significant amounts of Omega-3 fatty acids (1-3%) even though they also contain hydrogen sulfide as a highly toxic gas [10]. Moreover, algal species like *Anabaena* species, contains hepatotoxic compounds such as microcystins, nodularins, and neurotoxins such as anatoxin *a* [11, 12]. Researchers indicate presence of sulfate group with the degree of sulfation is the main key factor for anti-HIV activity. Considerably, nonsulfated and sulfated homo- and heteropolysaccharides isolated from algae like, *Nothogenia fastigiata* have revealed this activity [13]. Also, extracts and compounds like Cyanovirin-N isolated from *Agardhiella tenera* have shown significant activity against human immunodeficiency virus (HIV) and retroviruses like herpes simplex virus (HSV).

It is indicated that, *Ulva conglobata* has neuroprotective compounds with influences on murine hippocampal and microglial cells or Polysiphonia contain brominated phenols which are responsible for antibacterial activity [14, 15]. Considerably, compounds such as, Vascular Endothelial Growth Factor (VEGF) for treating emphysema and High Moblility Group Protein B1 (HMGB1) which activates immune cells are also produced and isolated from algae species [16]. Evidence of physiochemical studies supports antibacterial activity of micro and macro algae species as well , as an instance, three *Chaetomorpha linum*, *Enteromorpha compressa* and *Polysiphonia subtilissima* marine algae showed specific antibacterial activity on two Gram positive bacteria (*Bacillus brevis* and *Bacillus subtilis*) and three Gram-negative bacteria (*Escherichia coli, Vibrio cholerae* and *Shigella flexneri* [17]. In another study using minimum inhibitory concentrations (MIC) test, isolated epitaondiol monoacetate, stypotriol triacetate and stypodiol compounds from a brown alga *Stypopodium flabelliforme* showed antibacterial activities on *Staphylococcus aureus* , *Salmonella*

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typhimurium, *Proteus mirabilis, Bacillus cereus* , *Enterococcus faecalis* and *Micrococcus luteus* [18]. Evidences also showed extracts of *Ulva fasciata* (green algae) possess significant antiviral activity, further researches in this area led to isolation of an antiviral compound named UF-131. Moreover, 5-bromo-3, 4-dihydroxybenzaldehyde is another isolated compound from *Polysiphonia morrowii* which showed considerable antibacterial activities [19, 20]. Contemporary special attention has been made on natural products to discover novel antiviral, antibacterial and antifungal compounds. *The overall objective of this chapter is to present information on the discovered algal biomolecules against pathogenic microbes.*

2. Algae species with antimicrobial compounds

Algal antimicrobial activity has been recognized based on existence of compounds belonging to numerous chemical classes including phenols, fatty acids, indoles, acetogenins, terpenes, and *Volatile halogenated hydrocarbons* (VHHs). Acrylic acid is an antibiotic compound derived from algae species, and the marine micro algae *Phaeocystis pouchetii is introduced as the source of this valuable compound [21]*. Brominated pyrrole antibiotic C, isolated by Burkholder and colleagues [22] from Caribbean Sea grass or 2, 3-dibromo-4, 5-dihydroxybenzaldehyde and 2, 3-dibromo-4, 5-dihydroxy-1`-methoxytoluene isolated from *Rhodomela larix* are another identified bioactive marine metabolites with significant antimicrobial activities [23]. Evidences indicate that, the antimicrobial activity of extracts from the microalga *Chaetoceros muelleri* and *Dunaliella salina* had been related to its lipid composition, several fatty acids and other compounds such as chlorellin, neophytadiene and phytol [24]. There are several of suggestions due the antimicrobial action of derived fatty acids from algae which explain they may act upon multiple cellular targets, even though influence on cell membranes is the most feasible one. Damage of cell membrane leads to cell leakage and reduction of nutrient uptake and also inhibiting cellular respiration. Recall to this fact, antimicrobial activity of algae has been attributed to the presence of bioactive compounds, therefore a great rose on finding, isolating and screening different species of algae with significant anti pathogenic activities and interests on antibiotics from algal source has proceeded more rapidly than comparable studies.

3. *Asparagopsis taxiformis*

This red edible alga from the family of Bonnemaisoniaceae is *distributed* in Mediterranean region based on Cormaci and colleagues [25] report they are typically tropical to warm temperate species with diplohaplontic life cycle and cytotoxic, moreover antioxidant activities of them are well documented. These Algae have significant amounts of essential oil that mainly composed of bromoform and compounds such as chlorine, bromine, iodine-containing methane, ethanol, ethane, acetaldehydes, acetones, 2-acetoxypropanes, epoxypropanes, propenes, acroleins and butenones [26, 27]. *A. taxiformis* is a source of *halogenated* and aromatic volatile organic *compounds with strong* antimicrobial activity. The most abundant metabolites in *A. taxiformis* are oleic acid (51.33%) and n-hexadecanoic acid (42.87%) (Fig.1). It is reported that, extracts of *A. taxiformis* have antimicrobial activity against *Staphylococcus aureus, P. aeruginosa, B. subtilis, K. pneumoniae* and *Staphylococcus epidermidis, A. fumigates*, *A. terreus, A. flavus* and antiprotozoal activity on *Leishmania* [28]. Also, ethanol extracts of *Asparagopsis taxiformis* has inhibitory influences on *Vibrio alginolyticus*, *Vibrio vulnificus* and *Aeromonas salmonicida* subsp. Salmonicida [25].Quorum sensing (QS) known as a population density dependent gene regulation network which sends produced signals by bacteria via extracellular molecules to controls the biofilm formation. Considerably, observation of QS inhibitory compound in *A. taxiformis* points to its prospective use as an antifouling properties [29]. It is also reported that, the derived lipophilic compound from *A. taxiformis* primarily composed of pyrrole-2-carboxylic acid, pentadecanoic acid and octadecanoic acid play considerable protective role against microbes [30].

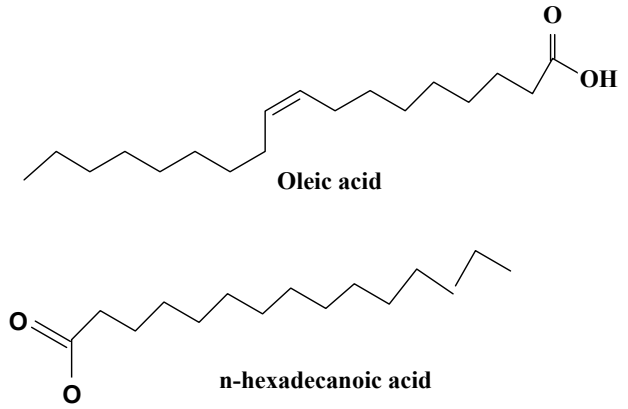
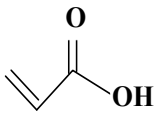


Fig 1. Chemical structures of oleic and n-hexadecanoic acids

4. *Phaeocystis pouchetii*

This alga from the family of Phaeocystaceae grows in temperature and higher latitude waters and releases compounds such as, acrylic acid and dimethylsulfide (DMS) during colony blooms. It is reported that the isolated α, β, γ, ∂-unsaturated aldehydes from *P. pouchetii* have cytotoxic influences on cell proliferation in human cells, diatoms and bacteria [31]. It is recognized that, there is a relationship between acrylic acid (Fig. 2) production by *P. pouchetii* and bacterial numbers, whereas by increasing the level of acrylic acid the viability and the number of bacteria decreases considerably. *P. pouchetii* excretes compound with significant influences on its surroundings, as an instance 2-trans-4-trans-decadienal a polyunsaturated aldehyde is identified by using mass spectrometry [32].



Acrylic Acid

Fig 2. Chemical structure of acrylic acid

5. *Spirulina platensis*

Spirulina is inhabited to the tropical regions and known to be one of the richest sources of proteins (60-70% of dry weight) and valuable resource for bioactive compound essential for human health. *S. platensis* contains bioactive compounds, including, alpha-linolenic acid, linoleic acid, stearidonic acid, eicosapentaenoic acid, arachidonic acid, docosahexaenoic acid and vitamins (B_1, B_2, B_3, B5, B_9, B_{12}, C, D, E and K), pigments (beta-carotene, zeaxanthin, chlorophyll a, xanthophylls, diatoxanthin and oscillaxanthin) [33, 34]. Heptadecane (39.70%) and tetradecane (34.61%) are documented as major components in essential oil of *S. platensis* (Fig. 3) [35]. It is reported that*, S. platensis* extracts have inhibitory influences on *Shigella flexneri*, *Salmonella typhi*, *Candida albicans*, *E. coli*, Bacillus sp., *P. fluorescens*, *A. hydrophila*, *V. alginolyticus, V. anguillarum*, *V. parahaemolyticus*, *V. harveyi* and *Edwardsiella tard [36]. It is known that compounds such as,* phycocyanobilin as NADPH oxidase inhibitors, zeaxanthin (particularly polar phenolic complexes) with highly antimicrobial activity, phycocyanin, allophycocyanin and sulfated polysaccharide compounds (calcium spirulan) as antioxidant and antiviral are abundant in *S. platensis* extracts [37]. Ergosterol and Glucosamine are fungal component related to fungal growth and biomass. It is claimed that, 1.15 mg phenolic compound/g can be obtained from methanolic extracts of *S. platensis* which have significant inhibition on glucosamine and wall polymers of *A. flavus* [38]. C-phycocyanin a protein-bound pigment isolated from *S. platensis* is capable to inhibit the growth of drug resistant bacteria including, *E.coli*, *K.pneumoniae*, *P.aeruginosa and S.aureus* [39]. It is known that, biotic and biotic stresses in different species results in enhancement of biologically active compounds, in this regard *S. platensis* cultivation under salt stress circumstances led to a significant alteration of algal metabolism as well as an enhancement or induction of antioxidant and antiviral compounds [40].

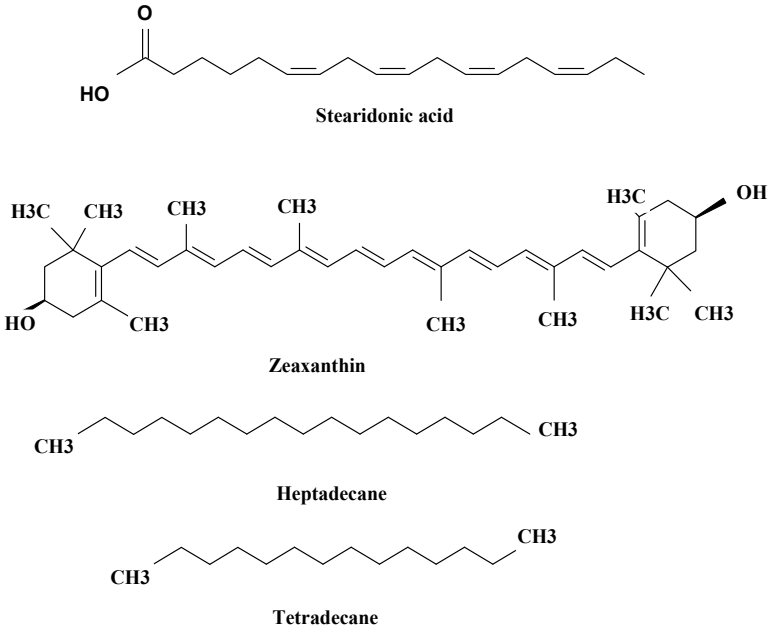


Fig.3. Chemical structure of some compounds derived from Spirulina platensis

6. *Cymopolia barbata*

C. barbata is a green Caribbean alga from the family of Dasycladaceae which can be found in shallow water. The extracts of this alga

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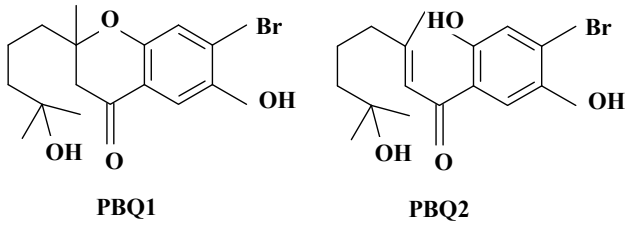

Fig 4. Chemical structure of PBQ1 and PBQ2

showed reliable pharmacological activity and compounds such as, 7-Hydroxycymopochromanone (PBQ1), 7-hydroxycymopolone (PBQ2), prenylated bromohydroquinones (3'-methoxy-7-hydroxycymopol, 3-hydroxycymopolone, 3, 7-dihydroxycymopolone, 7-hydroxycymopochromanone, 7-hydroxycymopochromenol), 1, 4-dihydroxybenzene, debromocymopolone, cymobarbatol and 4-isocymobarbatol [41, 42]. It is reported that, PBQ1 and PBQ2, have the potential to act as chemotherapeutic compounds, and hydroxyl moiety resident in PBQ2 acts selectively against the cancer colon cells (Fig. 4). Crude extract of *C. barbata* was found to block progesterone-stimulated reporter gene expression in cells transfected with the human progesterone receptor and purified cyclic epimeric bromohydroquinones (Cymobarbatol and 4-isocymobarbatol) from *C. barbata* reveal antimutagenic activity against *S. typhimurium* [43, 44].

7. *Ulva fasciata*

This green alga belongs to the family of Ulvaceae and it can frequently be seen in districts of fresh water runoff where nutrients are high. *U. fasciata* is also known as limu palahalaha and sea lettuce. Currently valuable compounds such as, guaiane sesquiterpene derivatives (guai-2-en-10a-ol and guai-2-en-10a-methanol), polyunsaturated fatty acids (stearidonic acid and α-linolenic acid), ulvanobiuronic acid 3-sulfate, bromophenolic and sphingosine-type compound isolated from *U. fasciata* [45, 46]. It is reported that, *U. fasciata* extracts possess antibacterial and antiviral influences on *Micrococcus luteus*, *B. cereus*, *B. subtilis*, *E. coli*, *A. hydrophila* , *P. aeruginosa, V. fischeri, V. harveyi, Chlorella vulgaris*, *C. sorokiniana*, and *Scenedesmus subspicatus* and Human Metapneumo Virus [47, 48] . In this regard, labda-14-ene 3 α, 8α -diol and labda -14ene-8α- hydroxy-3-one compounds isolated from *U. fasciata* showed inhibitory influences on the growth of *V. parahaemolyticus* and *V. alginolyticus*. *Also,* (E)-11- oxo-octadeca-12-enoic acid, (E) 11-hydroxy octadeca 12-enoic acids and 6-hydroxy-oct-7-enoic acid are novel identified fatty acids derived from *U. fasciata* which exposes antimicrobial activities [49].

8. *Stypopodium zonale*

This brown alga belongs to the family of Dictyotaceae and inhabited to shallow waters in tropical and sub-tropical regions. Different secondary metabolites such as, stypotriol, stypoldione, stypopodium, atomaric acid, stypoquinonic acid, 5′adesmethyl-5′-acetylatomaric acid, epitaondiol, and taondiol are isolated from *S. zonale.* Also stypoquinonic acid is another novel inhibitor of the Src-family protein tyrosine kinase Lck which is derived from *S. zonale.* Evidences indicate that*,* crude extracts of *S. zonale* inhibits the growth of *Aspergillus flavus, S. aureus,* Human Metapneumo Virus and Human Melanoma Cells [50-52].

9. *Sargassum wightii*

This marine macro brown alga belongs to the family of Sargassaceae, and existed in shallow water at the tropical regions and contemporary a wide range of bioactive compounds including, steroids, phenolic groups, alkaloids, saponins, anthroquinones and flavonoids are identified and isolated from it. 1-*O*-palmitoyl-3-*O* (6′-sulfo-α-quinovopyranosyl)-glycerol isolated from the methanolic extract of the brown seaweed *Sargassum wightii* is a novel bio-compound with antimicrobial activities against *Xanthomonas oryzae* [53]. Dioctyl phthalate (Fig.5) is another derived bioactive molecule from Chloroform-methanol (2:1) extracts of *S. wightii* with significant antimicrobial activities on *S. aureus, Proteus vulgaris, E. coli, S. typhi, S. paratyphi, S. typhiridium, K. pneumonia, Shigella sonnie, V. cholerae* and *P. aeruginosa* [54]. Moreover, Alginic acid isolated from *Sargassum wightii* exhibits potent anti-inflammatory and antioxidant activity. Senthil Rajan and colleagues [55] reported the antitumour influence of ethanol extract of *S. wightii* may be due to occurrence of sulfated polysaccharides, fucoidan and flavonoids as well as its antioxidant.

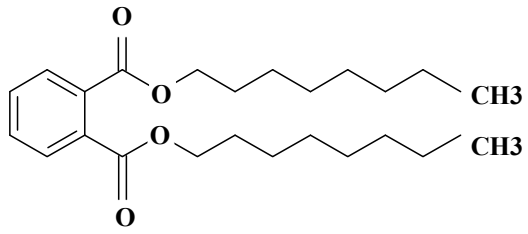

Fig 5. Chemical structure of Dioctyl phthalate

10. *Turbinaria ornate*

This tropical brown alga belongs to the family of Sargassaceae grows in Indian and Pacific Ocean in a variety of habitats including rocky intertidal, tide pools and deeper water. Presently compounds with considerable pharmaceutical activities including, Phloroglucinol, lectin, fucoxanthin, fucosterol, 29-hydroperoxystigmasta-5, 24 (28)-dien-3beta-ol, 24-hydroperoxy-24-vinyl-cholesterol were isolated from *T. ornate* which exhibit cytotoxicity against various cancer cell lines (Fig. 6) [56, 57]. *T. ornate* is considerably rich in phenolics, in this regard total phenolic content of it was measured 43.72 ± 1.63 mg gallic acid equivalents/g extract which suggests that *T. ornata* might be potent novel therapeutic and antimicrobial agents [58]. Literatures indicated that, *Cyclohexane, methanolic and n-hexane extracts of T. ornata are effective against S. aureus, S. epidermidis, E. coli and P. aeruginosa, A. niger and C. albicans* [59].

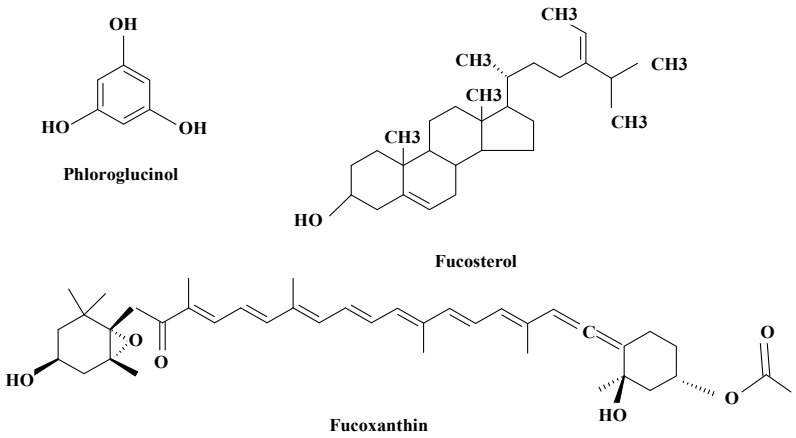

Fig 6. Chemical structure of some compounds derived from Turbinaria ornate

11. *Haematococcus pluvialis*

This freshwater alga belongs to the family of Haematococcaceae and compounds including fatty acids (lauric, myristic, palmitic, palmitoleic, margaric, oleic, lignoceric, gadoleic), vitamins (B_1, B_2, B_3, B_5, B_9, B_6, B_{12}, C and E) and carotenoids (astaxanthin, canthaxanthin, echinenone, lutein and β-carotene) are isolated from it. This alga is well known for its considerable content of a strong antioxidant identified as astaxanthin (3, 3′-dihydroxy-β, β-carotene-4, 4′-dione) [60, 61]. It is reported that, short chain fatty acids such as, butanoic acid, methyllactate plus simple phenols are responsible for *H. pluvialis* antimicrobial activity against *E.coli, S. aureus, C. albicans* and *A. niger,* moreover astaxanthin with vitamin C can diminish the *H. pylori* infection [62, 63].

12. *Laurencia brandenii*

This red alga belongs to the family of Rhodomelaceae inhibited to the tropical waters. *L. brandenii* contains diversity of fatty acids including, thunbergol, oxalic acid, allyl hexadecyl ester, 4-Dodecanol, allyl hexadecyl ester and cis- 9, 10-Epoxyoctadecan-1-ol but octadecadienoic acid (49.75%) and n-hexadecanoic acid (14.24%) are the major reported fatty acids in *L. brandenii* with inhibitory influences on *B. subtilis*, *E.coli*, *Micrococcus luteus*, *Rhodococcus rhodochrous*, *P.aeruginosa*, *S.aureus*, *Streptococcus pneumoniae, S. typhi,* and *V. cholera* [64, 65].

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13. Conclusion and future prospects

Production of biologically-active metabolites with antimicrobial characteristics from algal species is inherently linked to understanding their mechanism of production, molecular structure and biological influence. For progresses in this area of science different ideas must be utilized; in this regard (1) Endosymbiosis, antagonism to symbiosis, algal resistance mechanism, algal-algal, algal-bacterial recognition, signaling and interactions at the area of *phycosphere must be considered.* (2) Algal growth condition must be optimized and algae species must be cultivated in different media under influence of varied conditions (pH, temperature, light, initial algal density, usage of hormones and *Precursors*). (4) Proper extraction and purification methods must be introduced based on accuracy and easiness of use. (5) Responsible genes for algal antimicrobial activities must be identified and cloned. (6) Commercial development of highly valuable isolated compounds must be considered. (7) Academic world and industry must work closely.

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