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Review Article
Fresh Water Algae as a Potential Source of Bioactive Compounds for Aquaculture and Significance of Solvent System in Extraction of Antimicrobials

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Abstract
Algae are very important component of aquatic ecosystem, often seen growing at warmer temperature. The biomass constituents varies with available nutrient supply but algae are known for producing several biologically active compounds with antiviral, antibacterial, antifungal and anticancer activities. The extraction of bio active compounds differs according to the nature of solvent used. Phenolic compounds get extracted in polar solvent with differing yield, flavonoids in non-polar solvents, method of extraction such as soxhlet extraction yields heat stable components, where as cold extraction yields various lipid. In the present study investigation of the effect of different solvents, with increasing order of polarity on fresh water algae to develop alternative biodegradable natural compounds that are more environmentally acceptable alternate to antibiotics for aquaculture.

Key words: Aquaculture, bioactive, antibiotics, fresh water algae

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Aquaculture has developed to become the fastest growing food producing sector in the world. Majority of aquaculture are utilized food (85%) and the rest (15%) was utilized as live bait for fishing, ornamental products (pearls and shells), feed for carnivorous farmed species and marine worm. There has been a sustained growth in the fish supply during the last 50 years with an average growth rate of 3.2% each year. A large proportion of fish products come from small-scale producers in developing countries or low income deficit countries. The production of fish in China, Indonesia, India and Russia has increased while in other countries it has decreased. More than 80% of global aquaculture products are produced in fresh water. Currently, aquaculture accounts for 40.33% of the world's fish production. It is defined as the farming of fish, shellfish and aquatic plants in fresh or saltwater[1,2]. Around 600 aquatic species are raised in captivity worldwide. The Americas accounted for 4.30%, Europe accounted for 4.2%, Africa accounted for 2.2% and Oceania accounted for 0.30% of the world aquaculture production in the year 2010. However, Asia accounted for the majority (89%) of world aquaculture production in 2010. From its early development in Asia, aquaculture has undergone huge development and is highly diversified. Asian aquaculture fish production comprises of fin fishes (64.6%), molluscus (24.2%), crustaceans (9.7%) and other species (1.5%). Aquaculture consists of a broad spectrum of systems, from small ponds to large-scale, highly intensified commercial systems[3].

In recent years, with the increasing demand for fish product fish farming in pond, cages, pens in fresh water has become an important aquaculture industry in several countries (e .g., China, India, Indonesia, Vietnam and Norway). The global increase of aquatic animal production and farmed species has been associated with an increase in the number and spread of infectious diseases.

Directly and indirectly, diseases are the common cause of bankruptcy in aquaculture. They include both infectious and non-infectious (environmental, nutritional and genetic) problems. The non-infectious diseases are mainly due to management practices and are often limited to particular farms. However, infectious diseases have potential threat to whole industry. Sometimes human infections caused by pathogens transmitted from fish or the aquatic environment are quite common. Many a times quantification of the occurrence of these diseases is difficult because in most cases, typically gastrointestinal illness, go unreported, the symptoms usually do not last long and are self-limiting in healthy people. Few bacterial pathogen of fishes are extremely difficult to detect due to *in vitro* slow growth commonly associated with mycobacterial infections or infections largely caused by anaerobic pathogens. Consequently, the disease can last for years due misdiagnosis with inappropriate therapy[4].

ANTIBIOTIC USAGE IN INFECTION

It is common to use antibiotic compounds to treat bacterial diseases[5] to minimize significant stock losses and problems with animal mortality. All drugs legally used in aquaculture must be approved by the government agency responsible for veterinary medicine, for example, the Food and Drug Administration (FDA) in the USA. Some of antimicrobials authorized to be used in aquaculture are oxytetracycline, tetracycline, florfenicol and Sulfadimethoxine/ormetoprim. The most common route for the delivery of antibiotics to fish occurs through mixing the antibiotic with specially formulated feed. However, fish do not effectively metabolize antibiotics and will pass them largely unused back into the environment in feces. It has been estimated that 75% of the antibiotics fed to fish are excreted into the water[6]. Oxytetracycline, one of the most commonly used antibiotics in fish farms and hatcheries is very poorly absorbed through the intestinal tract of fish. It has to be administered at a high dosage rate of 100-150 mg per kg fish per day for 10-15 days. This treatment consequently causes the slow excretion of large amounts of this antibiotic, thus increasing the selective pressure which might lead to the selection of oxytetracycline-resistant bacteria in the gut. The presence of antibiotic-resistant bacteria in foods of animal origin is a potential health threat because resistance can be transferred among bacteria and antibiotic-resistant pathogens may not respond to antibiotic treatments. In a microbiological study of market products by Duran and Marshall[7]. The rise in bacterial antibiotic resistance and antibiotic residues has become global concerns and there is a need to develop alternative therapies for bacterial pathogens in animal production, especially in aquaculture. Search for new class of bioactive compounds with antimicrobial property is essential in aquaculture .

ALGAE AS POTENTIAL BIOACTIVE SOURCE

Algae are a very large and diverse group of autotrophic organisms which ranges from unicellular to multicellular forms. As photosynthetic organisms these groups play a key role in productivity of oceans and constitute the basis of marine food chain. Algae are ubiquitous in their habitat and may grow in waters of varying salinity, in fresh water, buildings, soils, brackish water, also living mutualistic with other organisms. They can be broadly divided into macroalgae (macroscopic algae) and microalgae

(microscopic algae). Presence of different pigment is one of the characteristics used to classify the different types of algae. The macro algae have a significant attraction as natural source of bioactive molecules with a broad range of biological activities, such as antibiotics, antiviral, anti tumor, antioxidant and anti-inflammatory evidence of phytochemical and pharmacological studies on algae is available. Algae are the source of amino acids, terpenoids, phlorotannins, steroids, phenolic compounds, halogenated ketones, alkenes and cyclic polysulphides. Marine algae are one of the largest producers of biomass in the marine environments. They produce a wide variety of chemically active metabolites in their surroundings, potentially as an aid to protect themselves against the other settling organisms. The first investigation of the antibiotic activity of algae was carried out by Pignatello *et al*.[8]. Evidence of phytochemical and pharmacological studies on algae is available in the literature with special references to terpenoids and steroids[9,10].

Micro algae represent unique opportunity for novel bioactive compounds although these groups of aquatic forms are recognized by their toxins. Extensive search is presently undergoing to find novel therapeutically useful agents. Due to their global adaptation in any hostile environment, metabolic plasticity under stressed vs. non-stressed conditions microalgae possess the extra advantage of triggering secondary metabolism paving way for several bioactive compounds.

IMPORTANCE OF EXACTIONS METHODS AND SOLVENT SYSTEM

However extraction methods plays a important role on isolation of bioactive compounds, secondary metabolites such phenolics, flavonoids, alkaloids, essential oil etc. These compounds have been extracted using solvent extraction methods where a high polarity solvent such as methanol is used[11-13]. The extraction mostly constitute of water soluble flavonoids and alkaloids. When polarity of the solvent was reduced using chloroform, hexane, ethyl acetate, butanol, it was found that more alkaloids, terpenoids could be separated. Bhagyavathy *et al*.[14] and Becher *et al*.[15] analyzed existence of bioactive compound in green algae *Chlorococcus humicola* through cold solvent extraction by different organic solvents acetone, benzene, chloroform, diethyl ether, ethyl acetate, ethanol, hexane and methanol, tested the extract antimicrobial activity against *E. coli*, *Pseudomonas aeroginosa*, *Salmonella typimurium*, *Klebsiella pneumonia*, *Vibrio cholera*, *Staphylococcus aureus*. Where maximum antimicrobial activity was recorded in ethyl acetate extract with 17 mm zone of inhibition at 25 µg/well accounting for the occurrence of lipophilic and phenolic compounds, lowest activity reported in acetone extract with zone of inhibition ranging from 7-10 mm, also ethyl acetate and benzene extract showed effective activity against Gram -positive population mainly due to high percentage of saturated and unsaturated fatty acid through GCMS studies. Rahul *et al*.[16] reported phytochemical studies of fresh water algae from Bhopal lake namely Bacillariophyceae, Chlorophyceae, Chrysophyceae, through organic solvents such as petroleum ether, acetone and methanol. Petroleum ether extract showed presence of lipidious compounds where as acetone extract accounted for alkaloids, terpenoids, flavonoids, glycosides and amino acids similarly methanol extracts answered except amino acids. Prarthana *et al*.[17,18] prepared cold solvent extracts of *Oscillatoria* and *Spirogyra* with increasing order of polarity viz methanol, ethanol, ethyl acetate, acetone, chloroform, diethyl ether, benzene, petroleum ether, hexane. Extracts are subjected to phytochemical tests for glycosides, alkaloids, saponins, flavonoids, tannins, phenols, cardiac glycosides, sterols, resins etc. Extracts showing positive for phenol, tannins, flavonoids were estimated for phenolic content, highest phenolic was recorded ethyl acetate extract of Oscillatoria and Spirogyra attributed to the polarity of the solvents, Oscillatoria extracts of ethyl acetate, methanol and ethanol, spirogyra extracts of diethyl ether, acetone and ethyl acetate showing phenolic, tannin and flavonoid content were test for antimicrobial sensitivity on *Aeromonas hydrophila*, *Streptococcus agalacitace Flavobacterium columnare*. Among all crude extracts ethyl acetate extract showed better result with zone of inhibition ranging from 10-24 mm against all pathogens.

Soxhalation using petroleum ether and maceration using hexane showed an entirely different profile of molecules obtained[19]. The extraction method definitely results in difference of secondary metabolites found in particular source. Hence, important plants which are a source of real potential candidates that can be effectively used in application should be screened for real bioactive components using more than on solvent profile or extraction method. Prakash *et al*.[20] evaluated antimicrobial activity of microalgae *Oscillatoria santa*, *Lyngbya birgeri*, *Oedogonium echinospermum*, *Spirogyra decimina, Spirogyra grantiana Spirogyra crassa*, *Siprogyra bioformis*, *Spirogyra condensate* against human pathogen namely *E. coli*, *Staphylococcus aureus*, *Salmonella typhimurium*, *Proteus vulgaris*, *Proteus mirabilis* and *Streptococcus pyogenes* through organic solvents methanol, ethanol, hexane by soxhlet extraction carried out at 60°C, showed reduced activity of extracts where only methanol and ethanol extracts of selected algae namely *Oscillatoria santa*, *spirogyra decimina*, *Spirogyra grantiana* showed considerable

activity against *Staphylococcus aureus*, *Proteus vulgaris* and *Proteus mirabilis*. Das *et al*.[21] evaluated *Euglena viridis* phytochemical constituents through soxhlet extraction by using different organic solvents like hexane, ethyl acetate, ethanol and methanol extraction was carried at 55-60°C, showed that only ethanol extract revealed antibacterial activity against *Psuedomonas putida, Psuedomonas aeroginosa, Psuedomonas flurescence, Aeromonas hydrophilla, Vibrio anguillarum, Vibrio alginolyticus, Vibrio fluvialis, Vibrio parahaemolyticus, E. coli* MIC concentration ranging from 50-100 μg mL^{-1}. Maruthi *et al*.[22,23] in his study natural on antimicrobial substance as a substitute for synthetic antibiotics analyzed, Oscillatoria and Spirogyra extracts are prepared in different solvents with increasing order of polarity. Extracts are subjected to phytochemical tests for glycosides, alkaloids, saponins, flavonoids, tannins, phenols, cardiac glycosides, sterols, resins etc. Extracts showing positive for phenol, tannins, flavonoids were estimated for phenolic content and tested for antimicrobial activity against pure cultures of *Aeromonas hydrophila*. Crude extracts subjected to GC-MS analysis reported many several bioactive compound showing antimicrobial, anti oxidant and anti fungal property. The cold extraction procedure adopted helped in the accountability of lipidous and hydrocarbon molecule.

BIOACTIVE COMPOUNDS FROM CYANOBACTERIA

Cyanobacteria have been identified as one of the most promising group of organisms from which novel and biochemically active natural products are isolated. Cyanobacteria such as Spirulina, Anabaena, Nostoc and Oscillatoria produce a great variety of secondary metabolites[24]. The only comparable group is actinomycetes, which has yielded a tremendous number of metabolites. The rate of discovery from traditional microbial drug producers like actinomycetes and hyphomycetes, which are in the focus of pharmaceutical research for decades, is decreasing and it is time to turn to cyanobacteria and exploit their potential. This is of paramount importance to fight increasingly resistant pathogens and newly emergent diseases[25]. Because *cyanobacteria* are largely unexplored, they represent a rich opportunity for discovery, the expected rate of rediscovery is far lower than for other better-studied groups of organisms.

Cyanobacteria produce a wide variety of bioactive compounds, which include 40% lipopeptides, 5.6% amino acids, 4.2% fatty acids, 4.2% macrolides and 9% amides. Cyanobacterial lipopeptides include different compounds like cytotoxic (41%), antitumor (13%), antiviral (4%), antibiotics (12%) and the remaining 18% activities include antimalarial, antimycotics, multi-drug resistance reversers, antifeedant, herbicides and immunosuppressive agents[26].

The current application of chemical compounds isolated from diverse classes of algae is enormous. Since 1975, three areas of research in aquatic natural products were emerged: toxins, byproducts and chemical ecology. Over 15,000 novel compounds were chemically determined. Focusing on bio-products, recent trends in drug research from natural sources suggested that algae are a promising group to furnish novel biochemically active substances[14]. To survive in a competitive environment, freshwater and marine algae developed defense strategies that resulted in a significant level of structural-chemical diversity from different metabolic pathways[27,28]. The exploration of these organisms for pharmaceutical purposes revealed important chemical prototypes for the discovery of new agents stimulated the use of sophisticated physical techniques and new syntheses of compounds with biomedical application. Moreover, algae were promising organisms for providing both novel biologically active substances and essential compounds for human nutrition[26,29]. Therefore, an increasing supply for algal extracts, fractions or pure compounds for the economical sector was needed[30]. In this regard, both secondary and primary metabolisms were studied as a prelude to future rational economic exploitation.

METABOLITES WITH ALGAECIDAL ACTIVITY

The discovery and application of natural and natural based compounds has been tried to control harmful algae in aquatic systems as an alternative to synthetic algicides. The reported studies involve lysine and its analogs[25], ferulic acid, transcinnamic acid, anthraquinone,1,3-dichloronaphthoquinone[31], bacillamide[32] fischerellin[33] B, 12-epi-hapalindole[34] F oxygenated fatty acids and potassium ricinoleate[35] harmane and rutacridone epoxide[36].

The algaecidal activity of the cyanobacteria has been principally observed in diverse genera such as *Anabaena*, Microcystis[37], *Calothrix, Fischellera, Nostoc*[38],*Nodularia*[39] and *Phormidium*[40]. In the *Oscillatoria* genus, the inhibiting effect of a non-polar natured extract was inhibiting effect of a non-polar natured extract was observed over the growth of the cyanobacterium *Anacystis nidulans* and of *Brassica compestris* and *Coriandrum sativumplants* (inhibitor of photo system II), interestingly this extract wasn't toxic in mice

atintraperitoneal dosis[41] of 16 Lg mL^{-1}. Examples of algaecidal compounds peptide structure showing potent biological properties at lMor Lg mL^{-1} levels, spiroidesin (*Anabaena spiroides*) with activity against toxic cyanobacteria *Microcystis aeruginosa* (IC50 =1.6910-6M)[50]. In contrast, *M. aeruginosa* produced kasumigamide[42], other peptides are nostocyclamide and nostocyclamide M (Nostoc sp. 31) with inhibitory properties (IC50 = 0.1 lM) against *Anabaena*[43,44] and pahayakolide A (Lyngbya sp.) which showed effect against *Chlamydomonas Ev-29* green algae at 6.8 lM[45,15]. Nostocine A is an unusual pyrazolo triazine isolated from Nostoc spongiaeforme with toxic effect comparable to paraquat against *Anabaena, Nostoc commune, Oscillatoria* and green algae *Chlorella and Dunaliella* at MIC values of 5-30 lM[46]. Harada *et al.*[47] Kaya *et al.*[48] and Kim *et al.*[49] found that extracts of the genus *Polygonatum* inhibited the growth of several freshwater algae (such as *C. vulgaris*, *Scenedesmus* sp. and *M. aeruginosa*) as well as duckweed. The results demonstrated that L-2-azetidinecarboxylic acid (AZC) selectively inhibited algal growth at low concentrations. The allelopathic effects of three macroalgae, namely *Ulva pertusa, Corallina pilulifera* and *Sargassum thunbergii*, on the growth of the microalga *Skeletonema costatum* (Grev.) were evaluated by Wang *et al.*[50]. They demonstrated that the growth of *S. costatum* was strongly inhibited when fresh tissues, dry powder and aqueous extracts were used, (EC_{50} ranged from 0.45 to 3.50 g FW/L). Allelopathic effects of the green macroalgae *Ulva lactuca* on the growth of three species of red tide microalgae, *Heterosigma akashiwo, Alexandrium tamarense* and *Skeletonema costatum* were studied by Nan *et al.*[51]. They showed that *U. lactuca* exhibits negative allelopathic effects on harmful bloom-forming microalgae.

More algaecidal alkaloids are fischell-erin A[52,53] and[54,55,33], fischellerin[56] B and nostocarboline (Nostoc 78-12a)[11].

Antiprotozoal metabolites: There are only six antiprotozoal metabolites reported from freshwater microalgae. Antiplasmodial indole [3,2-j] phenanthridines named calothrixins A and B (Calothrix sp.) inhibited *Plasmodium falciparum* FAF6 growth at IC_{50} = 58 and 180 nM while chloroquine used at the same assay displayed growth inhibition[16] at 83 nM. Other natural product from freshwater algae with moderate antiprotozoal activity against *P. falciparum* clone KI (IC_{50} = 1.5 Lg mL^{-1}) and NF54 (IC_{50} = 2.4 Lg mL^{-1}) is ambigol C, which was isolated from *Fischerella ambigua*[57]. Furthermore, aerucyclamides A-D (*M. aeruginosa*) were reported from microalgae between[58,59] 2005 and 2008 but only aerucy-clamides C and D exhibited antiplasmodial properties.

Insecticidal and larvicidal metabolites: There are some examples of natural products from freshwater microalgae with insecticidal activity most important being those isolated from *Fischerella* genus: 12-epi-hapalindole C isonitrile, 12-epi-hapalindole E isonitrile, 12-epi-hapalindole J isonitrile and hapalindole L. These compounds killed 100% of the larvae of the dipteran *Chironomus riparius* within 48 h at\37lM[60]. A sesquiterpene with activity against the same dipteran was eremophilone ,from *Calothrix sp*. PCC 7507, which showed acute toxicity (LC50) against insects at 29 lM and *Thamnocephalus platyurus* (crustacea) at 22 lM, the compound was not toxic for *Plectus cirratus* (nematoda)[45]. Another alkaloid with insecticidal properties is 2(R),5(R)-bis(hydroxy-methyl)-3(R),4(R)-dihydroxypyrrolidine (DMDP, 35), isolated from *Cylindrospermum licheniforme* and higher plants, it showed be a glucosidase digestive inhibitor of aquatic insects and crustacean grazers (*Thamnocephalus platyurus*)[61]. There are several reports about the potential in the vectors control of disease such as malaria, dengue, encephalitides and filariasis through the use of microalgae and algae. Effects of them could be the toxicity to aquatic stages of mosquitoes, reduction of population by algae's indigestibility or modification of the reproductive cycles[12,62-66]. The use of microalgal hepato and neurotoxins as mosquito control agents is not recommended for environmental implications. However there are larvicides from cyanobacteria, which are not hepato and neurotoxic, an example was a compound partially purified from *O. agardhii*, which was highly toxic in larvae of *Aedes aegypti*[67]. Studies in the same species of microalgae revealed a toxic mixture to larvae of *Aedes albopictus,* unsaturated (oleic, linoleic and c-linoleic acids) and saturated (myristic, palmitic, stearic acids) fatty acids were found in the mixture[68].

Antimicrobial metabolites: There are several chemical groups of microalgae's metabolites with antimicrobial activity including fatty acids, alkaloids, aromatics, macrolides, peptides and terpenes. Extract with pronounced activity were obtained from *Chondrococcus hornemanni* and the active component was found in a mixture containing dihalogenated monoterpenes. Acrylic acid appeared to be responsible for the antimicrobial activity of *Gracilaria corticata* and *Ulva lactuca*. Extracts from 65 different sea water and fresh water algae were screened for *in vitro* antimicrobial activity by Perez *et al.*[57]. The result indicated that nine algae showed activity against *Staphylococcus aureus*, nine against *Staphylococcus pyogenes*, four against *Pseudomonas aeruginosa,* one against *Proteus vulgaris,* three against *Escherichia coli,* three against *Aspergillus fumigatus* and two

against *Candida albicans*. The most active extracts were those of the *Rhodophytae*. None of the extracts from the fresh water algae showed activity against microorganisms at concentration up to 50 mg mL^{-1}. The antimicrobial activities of extracts of three fresh water green algae (*Spirogyra* sp., *Chara* sp. and *Cladophora* sp.) and 11 marine algae green: *Enteromorpha linza, Ulva lactuca, Cladophora coelothrix* and *Codium tomentosum*, brown: *Colpomenia sinuosa* and *Padina pavonica*, red: *Gelidium* sp, *Laurencia obtusa*, *Polysiphonia* sp., *Hypnea musciformis* and *Galaxuara rugosa* were screened against *Escherichia coli* and *Staphylococcus aureus*. They found that the fresh water algal extracts had the highest antimicrobial activity against both bacteria. While the marine algal were active against *S. aureus* only. The n-Hexane, ethyl acetate and methanol extract of *Sargassum desfontainesii, Halopteris scoparia, Stypopodium zonale, Codium intertextum* and *Ulva rigida* (collected from the littoral of Tenerife) were screened for antibacterial and antifungal activities by Febles *et al*.[58] and Mesmar and Abussaud[69]. The results indicated that the methanol extracts showed the most potent antibacterial activity, particularly against *Bacillus cereus* and *B. subtilis*. The extracts of brown and green seaweed did not exhibit antifungal properties. The methanol extract of *Codium intertextum* showed activity against *Saccharomyces cerevisiae* and three species of *Candida*.

Laxaphicins B and C (Anabaena laxa) are lipopeptides that showed inhibitory activity against *Aspergillus oryzae, Candida albicans, Penicillum notatum, Saccharomyces cervisiae* and *Trichophython mentagrophytes.* The test was made by disk assay (50 lg/disk) and these com-pounds showed also significant cytotoxic property[70]. Pahayokolide A (*Lyngbya* sp.) is a peptide with antimicrobial activity which inhibited the growth of *Bacillus megaterium* (MIC = 5 Lg mL^{-1}) and *Bacillus subtilis* (MIC = 5 Lg mL^{-1}) and showed cytotoxicity over six cell lines (IC50\6 IM)[55,33]. Fatty acids such as a dimorphecolic, coriolic and linoleic acids from *Oscillatoria redekei* were capable of inhibiting the growth of the Gram-positive bacteria *B. subtilis, Micrococcus flavus* and *Staphylococcus aureus*, although their activities were moderate with MIC values[71] of 75-100 Lg mL^{-1}. A more active fatty acid was linolenic acid, produced by *Fischerella* sp., which also demonstrated growth inhibition of *Escherichia coli*, *Enterobacter aerogenes*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *S. aureus* with MIC values[72] of 4-16 Lg mL^{-1}. More non-polar antimicrobial compounds were propanoic and butanoic acids as major components of an active mixture (MIC = 3-16 mg mL^{-1}) against *Aspergillus niger*, *C. albicans*, *E. coli* and *S. aureus*, this was obtained from *Haematococcus pluvialis*[73]. From *Fischerella* genus was isolated parsiguine, a non polar cyclic polymer with activity against *Staphylococcus epidermidis* (MIC = 40 Lg mL^{-1}) and *Candida krusei* (MIC = 20 Lg mL^{-1})[74]. Other antimicrobials isolated from the same genus were *Fischellerin* A[57-59], ambigols A, B[72] and ambiguine A-F , H-I, K-O isonitriles[75-77]. Many substances with antimicrobial potential have been isolated from *Nostoc* genus[78,20], some of them are diterpenoids with important activities. For example, 4-[(5-carboxy-2-hydroxy)-benzyl]-1,10-dihydroxy-3,4,7,11,11-pentame-thylocta hydrocyclopenta\a[naphthalene showed growth inhibition of *E. coli, E. aerogenes, P. aeruginosa, S. aureus, S. typhi* (MIC = 0.5-16 Lg mL^{-1}) and *M. tuberculosis* H37Rv (MIC = 2.5Lg mL^{-1})[21]. Other significant antimicrobial compounds are noscomin[20], comnostins A-E[79] and 8-[(5-carboxy-2,9-epoxy)benzyl]-2,5-dihydroxy-1,1,4a,7,8 pentamethyl-1, 2, 3, 4, 4a, 6, 7, 8, 9, 10, 10a dodeca hydrophenanthrene, 1,8-dihydroxy-4-methylanthraquinone 4-hydroxy-7-methylindan-1-one[80]. Several of these compounds showed selective and potent antibacterial properties, which were equal to chloramphenicol and tetracycline when were tested *S. epidermis* and *E. coli*, respectively[81,41]. More antimicrobials from *Nostoc* genus are nostofungicidine with activity against *Aspergillus candidus* (MIC = 1.6 Lg mL^{-1})[82] and carbamidocyclophanes A-C, which displayed more cytotoxicity than antimicrobial properties[78]. *Hapalosiphon fontinalisis* recognized as producer of fungicidal compounds, some of them being fontonamide, anhydrohapaloxindole A , hapalindoles C-H, J-K , L , M-Q and T-V[83,84]. In the same way, welwitindolinone A isonitrile and N-methylwelwitindolinone C isocyanate have been isolated from *H. welwitschii* and *Westiella* genus[85]. Antimicrobials identified from *Scytonema* genus are cyanobacterin[86,20], scytophycins A-E[21], tolytoxin[79] and scytoscalarol, a guanidine-bearing sesterterpene[80]. Macrolide 99 showed selective and potent fungicidal activity against two yeast and 12 filamentous fungi, their MIC values were between[81] 0.25 and 8 nM, Metabolites 95 and 98 were isolated from *Cylindrospermum muscicola* together with their also fungicidal derivates 6-hydroxyscytophycin B and 6-hydroxy-7-methoxy-scytophycin E (Nostocaceae family)[43]. Furthermore, 95 and 98 were cytotoxic agents with potential for killing drug-resistant tumor cells[38]. Active compounds against *S. typhi* were isolated from *cyanobacteria Microcoleus lacustris*, 20-nor-3a-acetoxy-abieta-5,7,9,11,13-pentaene and 20-nor-3a-acetoxy-12-hydroxy-abieta-5,7,9,11,13-pentaene whose MIC values were 61.4 and 46.2 Lg mL^{-1}, respectively[76].

Moderate antimicrobial activity has been observed for green microalgae such as *Euglena viridis*[82] and *Spirogyra varians*[87]. From *S. varians* was identified pentagalloyl glucose as responsible of its antimicrobial effect against *B. subtilis* and *Micrococcus flavus*.

COMPOUNDS WITH OTHER ACTIVITIES

The nematicidal properties of the microalgae against *Meloidogyne species* have been reported with extracts or direct application of organisms such as *Aulosira fertilissima*[88], *Microcoleus vaginatus*[89] and *Oscillatoria chorine*[55].

The study carried by Prarthana *et al*.[17,18] exploring use of cold solvent extracts of Oscillatoria and Spirogyra with increasing order of polarity viz methanol, ethanol, ethyl acetate, acetone, chloroform, diethyl ether, benzene, petroleum ether, hexane, has yielded different bioactive constituents such as Glycosides, alkaloids, saponins, flavonoids, tannins, phenols, cardiac glycosides, sterols, resins etc. Extracts accounting positive for phenol, tannins, flavonoids were estimated for phenolic content, highest phenolic was recorded ethyl acetate extract of Oscillatoria and Spirogyra attributed to the polarity of the solvents, Oscillatoria extracts of ethyl acetate, methanol and ethanol, spirogyra extracts of diethyl ether, acetone and ethyl acetate showing phenolic, tannin and flavonoid content were test for antimicrobial sensitivity on *Aeromonas hydrophila*, *Streptococcus agalacitace Flavobacterium columnare*. Among all crude extracts ethyl acetate extract showed better result with zone of inhibition ranging from 10-24 mm against all pathogens. The crude extract showing good antimicrobial sensitivity were subjected to GC-MS analysis reported many several bioactive compound showing antimicrobial, anti oxidant and anti fungal property. Oscillatoria ethanol extracts contained diethyl phthalate with peak 4.72 n-Hexadecanoic acid with peak 5.26 hexadecanoic acid ethyl ester with peak 34.00 octadecanoic acid,17-methyl-,methyl ester with peak 1.48. Simultaneously Oscillatoria ethyl acetate extracts contained diethyl phthalate with peak 0.13 n-Hexadecanoic acid with peak 0.68 Bis (2-ethylhexyl)phthalate with peak 98.40. Similarly Oscillatoria methanol extracts contained diethyl phthalate with peak 3.70 n-Hexadecanoic acid with peak 51.20 Bis (2-ethylhexyl)phthalate with peak 43.80.

Another fresh water extract of Spirogyra in Diethyl ether contained Bis(2-ethylhexyl)phthalate with peak 92.54, n-Hexadecanoic acid with peak 2.35, Dibutyl phthalate with peak 1.56, tetradecanoic acid with peak 1.93, butylated hydroxytoluene with peak 1.36. Consequently Spirogyra acetone extracts yielded tetradecanoic acid with peak 16.46, pentadecanoic acid with peak 2.55, n-Hexadecanoic acid with peak 29.02, Trans-13-Octadecenoic acid with peak 2.70, octadecenoic acid with peak 11.17, Bis(2-ethylhexyl)phthalate with peak 21.16. Similarly spirogyra ethyl acetate extracts contained diethyl pimelate with peak 0.62, diethyl suberate with peak 0.89, nonanedioic acid, dimethyl ester with peak 1.98, tetradecanoic acid with peak 4.87, n- Hexadecanoic acid with peak 10.81, hexadecanoic acid, ethyl ester with peak 1.15, octadecanoic acid with peak 1.79, Bis(2-ethylhexyl)phthalate with peak 65.86, due to cold extraction procedure , extracts accounted for several lipidous and hydrocarbon molecule. The discovery has identified several antimicrobial compounds through cold extraction in increasing order of solvent polarity. The current study could help to explore many bioactive compounds could be used as substitute for antibiotics in aquaculture.

CONCLUSION

Algae have a significant attraction as natural source of bioactive molecules with a broad range of biological activities, such as antibiotics, antiviral, anti tumor, antioxidant and anti-inflammatory evidence of phytochemical and pharmacological studies are available. They produce a vast majority of chemical metabolites to the surrounding. Some of the bioactive constituents obtained from algae are amino acids, terpenoids, phlorotannins, steroids, phenolic compounds, halogenated ketones, alkenes and cyclic polysulphides. Cold extraction and using different organic solvents of increasing order of polarity has identified many lipidous compounds with antimicrobial properties, can be used as potential target for treating infections in aquaculture.

Normally in fresh waters, the micro green algae and cyanobacteria are recognized by their toxins. These toxins include a diversity of nitrogen-rich alkaloids and peptides, feared by man but also have a huge potential for the development of pharmaceutical and agricultural applications. Exaction of bioactive compounds largely depends on solvent and method adopted for extraction.

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