Review Article

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Applications of Algal Based Therapeutics in Human Health

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Abstract:

Algae are microorganisms abundant in our world's ecosystems and are present in the form of pond scum, seaweed, phytoplankton, cyanobacteria etc. The algae produce multiple primary and secondary metabolites as a result of their intrinsic biochemical pathways. The metabolites are biologically active molecules such as polysaccharides, proteins, fatty acids, pigments, vitamins, minerals and other further complex molecules. These compounds can be harnessed for pharmaceutical applications due to their inherent properties or derivatives which possess desired properties such as antioxidant, anti-inflammatory, antitumour, anticancer, antiviral and antimicrobial characteristics. They have benefits of being less toxic, biodegradable and vastly available due to the large number and variety of algae present in our world. This review paper discusses the properties of such bioactive molecules as well as their current and potential applications. The application areas discussed are drug delivery systems, cancer, COVID-19, cardiovascular diseases and as an alternative to antibiotics.

Keywords: algae, bioactive compounds, pharmaceutical applications, sulfated polysaccharides, algal metabolites

1. Introduction

Algae are photosynthetic microorganisms which all aquatic ecosystems depend upon, either directly or indirectly. They can be present in the form of pond scum, seaweed, phytoplankton etc and are the base of the food chain in all the ecosystems they are present in, for the protein needs. Depending on the level of size, pigment, and structurisation, the algae can be categorised into two categories which are macroalgae and microalgae. Macroalgae are multicellular and organized structures which resemble plants while microalgae are much simpler unicellular organisms [1].

Specifically, microalgae are capable of producing multiple varieties of bioactive molecules which can be directly obtained from primary metabolites such as proteins, essential fatty acids, pigments, polysaccharides, vitamins and minerals. These molecules have ample potential and benefits in the

pharmaceutical industry such as: antioxidant, anti-inflammatory, antitumor, anticancer, antiviral and antimicrobial products [2]. In most microalgae, the bioactive molecules are concentrated in the biomass,

but could also be excreted into the medium and then obtained [3].

In 2021, the global markets for algae products were $4.7 billion and was projected to increase with a cumulative annual growth rate of 6.3% between 2021-2026, and reach $6.4 billion by 2024. Some of the major global players have been AlgaTechnologies Limited, BASF SE, Cellana Incorporated, Cyanotech Corporation, DIC Corporation, and E.I.D Parry (India) Limited [4]. Majority of this market is for pharmaceutical and nutraceutical applications of algal products.

In recent years, especially the past decade or so, microalgae-derived nanoparticles have been used in drug delivery systems for their advantages of being less toxic, and having greater biodegradability and active surface area. Such systems are used to target specific drugs or genes to specific cells, such as cancer cells [5].

In light of the COVID-19 worldwide pandemic, it is imperative to find effective treatments quickly. Various studies with various microalgae and their derived products suggest that they could be an effective source for antiviral products effective against the coronavirus [2].

1.1 Origins of algal therapeutics

Algae have been used as food, folk cures, colours, and fertilizers for centuries. The first scientific studies on microalgae began around the end of the nineteenth century, when the microbiologist Beijerinck succeeded in producing pure cultures of *Chlorella vulgaris*. Microalgae had initially been used in research, such as photosynthesis studies [6]. As mass food manufacture grew in popularity in the early 1900s, its components were harnessed industrially. Even today, hydrocolloids such as alginate, carrageenan, and agar are the most extensively utilised components in culinary, pharmaceutical, and biotechnological applications due to their gelling properties [7]. Seaweeds have long been used in traditional and folk medicine, although their utility in contemporary medicine was only discovered around 1950 1. Algae are one of the largest producers of novel chemicals of marine origin, particularly those with anticancer and cytotoxic potential, among marine species. In both in vitro and in vivo settings, these compounds revealed the ability to induce particular inhibitory actions on a number of critical cellular processes, including apoptotic pathways, angiogenesis, migration, and invasion, indicating their potential for application as anticancer medicines [8].

In Table 1, we have summarised some of the bioactive compounds and their applications discussed in this paper for convenience of reading.

2. Drug delivery systems

Over the last few decades, multiple drug delivery systems have been proposed as treatment strategies in hopes of hindering the development of resistant strains of pathogens. An integral part of this approach is the sustained release of the antibiotic at an accurate time and location, avoiding unnecessary side effects or inducing bacterial resistance. The latest technologies have used nanoparticles, which proven to be effective, but have a concern of probable toxicity, limited drug loading capabilities and burst effects. Efforts have been focused on marine algae derived bioactive molecules since these algae possess cell walls rich in sulfated polysaccharides [9]. Carrageenan, derived from red algae, and fucoidan, derived from brown algae, are examples of such polysaccharides.

Micro- and nanoparticles are formulated using negatively charged sulfated polysaccharides. Such carriers are used to enhance the pharmacodynamic and pharmacokinetic properties of drug molecules. The sulfated polysaccharides have a tendency to form complexes with cationic polymers resulting in the formation of nano-sized carriers. This structure is beneficial since it allows for molecular level interactions between the drugs and the carrier [10].

K-carrageenan nanoparticles showed greater encapsulation efficiencies with model molecules, like glucose oxidase. When treated with various enzymatic and physiological solutions, a sustained release was observed with k-carrageenan/chitosan nanoparticles exhibiting the lowest release rate. In another study, it was observed that fucoidan/chitosan nanoparticles exhibited a pH-sensitive behaviour, allowing for sustained release of curcumin (an

antitumor drug) in solutions mimicking the gastrointestinal environment. Such characteristics have proven effective and efficient for encapsulation for a broad spectrum of molecules including DNA, protein, and anticancer drugs, antibiotics [10].

Carrageenan/chitosan microspheres have been used to encapsulate local anaesthetic agents and insulin [11]. This is extremely crucial for insulin as it allows the development and administering of an oral diabetic therapy which produces a prolonged hypoglycaemic effect [12]. A further study suggested the use of k-carrageenan/folic acid microparticles to deliver doxorubicin to cancer cells, which seemed to reduce cell viability in human osteosarcoma cell lines. Fucoidan/chitosan microspheres witnessed great applicability in protein delivery [13] and have majorly aided in the release and encapsulation of ofloxacin, a broad-spectrum antibiotic [10].

Such microspheres show scope in targeted drug delivery systems too. The addition of a ligand which displays selective affinity for cell receptors can enable the molecules to target delivery sites, making sulfated polysaccharide carriers viable for targeting cancerous cells and targeting macrophages to trigger immune responses [10]. A study conducted with alveolar macrophages observed the effects of different functional groups on the microsphere surfaces. It was noted that many of these functional groups were modified to display hydroxyl, carboxyl or sulfate residues The microsphere surfaces were observed to be negatively charged and easily taken up by macrophages [14]. Particularly, carrageenan was found to increase the binding and killing abilities of macrophages [15], which proves effective in therapies dealing with elimination of intracellular macrophage pathogens, such as in tuberculosis and leishmaniasis. Fucoidan too shows immunomodulatory effects, enhancing the production of pro-inflammatory cytokines on infecting macrophages with strains of *Leishmania donovani fucoidan* [10].

Table 1: A comparison of different algal bioactives

Sr. No	Bioactive Compound	Algae	
1	Carrageenan	*Galaxaura marginata, Eucheuma serra*	
2	Fucoidan	*Fucus vesiculosus*	
3	Ulvan	*Ulva lactua*	Antiviral prop
4	Galactan	*Aghardiella tenera, Schizymenia binderi*	Antiviral prop
5	Peptides	*Chlorella vulgaris*	Antioxidant properties; ir adenocarcinor
6	Cryptophycin 1	*Nostoc sp GSV 224*	Anti-tumour action 3
7	C-phycocyanin	*Arthrospira platensis*	Enhances anti for treatment
8	Lectins	*Galaxaura marginata, Eucheuma serra*	Antibacterial bacteria
9	Scytovirin	*Scytonema varium*	Antiviral activ
10	Griffithsin	*Griffitsia sp.*	Antiviral activ
11	Bromophenols	*Chlorophyceae, Rhodophyceae, Phaephyceae*	Antibacterial properties; an antimalaria pr properties
12	Diterpenes	*Rhizoclonium Hieroglyphicum, Dictyota pfaffi, Dictyota menstrualis*	Antibacterial
13	Phlorotannin	*Eisenia bicyclis, Ecklonia cava*	Antibacterial properties, an
14	Glycolipids	*Nannochloropsis gaditana, Isochrysis galbana*	Antitumour p
15	Docosahexaenoic Acid	*Arthrospira platensi, Spirulina, Arthrospira maxima*	Macronutrien
16	Eicosapentaenoic Acid	*Arthrospira platensi, Spirulina, Arthrospira maxima*	Macronutrien
17	Carotenoids	*Chlorella zofingiensis; Chlorococcum sp.*	Antitumour p properties, an properties

3. Cancer

Cancer is a leading cause for death across the globe. Malignant tumours, frequently referred to as an uncontrolled cellular reproduction, are related to great pathologic changes. owing to such high levels

of impact, considerable attention has been paid to eradicate cancer.

Chemotherapy is usually the go to treatment to cure cancers; these drugs can extend the survival time of patients by destroying or at least inhibiting growth of tumour cells. The significant side effects of these drugs usually deteriorate the quality of the patient's life to a great extent. Hence there is an urgent need to look into anticancer agents from various different resources. [16]

Lately, research on cancer treatment has focused on molecular targeted therapies, and the anti-cancer activities of many phytochemicals have been studied and researched [17]. Many natural antitumor composites are generally synthesised by algae 16. Microalgae phytochemicals have an array of phenolic classes that display effective and important biological activities with great potential [18,19].

Microalgae display their anti-cancer effects via complex mechanisms resulting from their significant structural diversity, which necessitates numerous interactions and reactions. Microalgae with the help of their bioactive heighten the host's defence by activating the immune system, improving natural killer-cell activity and inhibiting tumour growth. Thus, microalgae have been frequently proposed as of late to hinder carcinogenesis [16]

As discussed above various algae produce important metabolites some of which can provide significant anti-tumour activities, below we have categorised this anti-tumour abilities on the basis of molecule type for better understanding and clarity.

3.1 Antitumor capacity of algal carotenoids

Carotenoids are a well-researched type of antioxidant and are also known to show antitumor activity. Recently, their use in the treatment of colorectal cancer alongside the chemotherapeutic agent 5-fluorouracil has assisted in complete remission, while partial remission was detected post treatment with chemotherapy alone. Hence, microalgae are discussed as potential natural drugs for inhibiting and treating reactive oxygen species (ROS) - related diseases [20].

Astaxanthin, a microalgal derived carotenoid, is known for its characteristic antitumor capabilities [21]. It has been observed to prevent cellular proliferation in particular cell lines such as human gastric cancer cell lines. Astaxanthin is an effective antioxidant, furnished with the ability to prevent cytotoxicity effectuated by oxygen species. It even plays a role in stimulating hepatic xenotoxic-metabolizing enzymes, and enhancing tumour immunity [16].

3.2 Antitumor capacities of algal polysaccharides

Fucoidan is endowed with numerous biological properties of which anti-inflammatory, antiangiogenic, immunomodulatory and antiviral properties are just a few examples [22]; in accordance with the species of algae it is obtained from these properties of fucoidan vary with respect to its chemical characters. Fucoidan extracted from *Fucus vesiculosus* has anti-tumour potential which may be partially due to its anti-angiogenic capacity [16].

3.3 Antitumor capacity of algal peptides

Peptides are also known to display various types of biological activities [16]. For example, peptides isolated from *Chlorella vulgaris* are equipped with the ability to inhibit gastric adenocarcinoma cells (AGS) along with prevention of subsequent cell growth. This peptide exhibited heightened antioxidant properties in response to peroxyl radicals. This ROS species attacks biological molecules like lipids, DNA, and proteins, which can lead to degenerative changes in some cases even tumours [23].

Cryptophycin 1 is a peptide extracted from Nostoc sp GSV 224, a blue-green algae, which exhibits anti-tumorigenic activity against human tumour cell lines. It was noted that the semi-synthetic form of Cryptophycin, Cryptophycin-8 presented better antiproliferative action [23].

4. COVID-19

The novel coronavirus (2019-nCoV), more commonly known as the coronavirus disease 2019 (COVID-19), is a pathogenic respiratory tract illness caused by the severe acute respiratory syndrome coronavirus [2] (SARS-CoV-2). Since the end of 2019, SARS-CoV-2 infections have developed varied symptoms, differing between individual cases, ranging from asymptomatic conditions to life threatening and mortality [24]. Algae derived bioactive molecules possess antiviral, anti-inflammatory and anti-tumour properties which can aid in combating COVID-19 [24-27].

It has been agreed upon that the major mechanism by which the virus causes severe symptoms is cytokine storm (CS). Cytokine storm refers to the phenomenon that occurs when the etiologic agent SARS-CoV-2 provokes monocytes and macrophages to release excessive amounts of pro-inflammatory cytokines, namely tumour necrosis factor (TNF)-α and interleukin (IL)-6. A large influx of TNF-α and IL-6 destabilizes the endothelial cell networks and causes vascular damage, capillary damage, alveolar damage, apoptotic cell death and organ failure. Specifically, this is critical for destroying the lung's epithelial and endothelial linings, possible leading to acute respiratory distress syndrome (ARDS), requiring admission to intensive care units and is the main cause of death of patients with COVID [24,25]. Hence, anti-TNF therapy is vital to reduce capillary leak due to inflammatory cytokines for the preservation of lung function of COVID-19 patients.

Multiple studies have been conducted which show that aqueous extracts of *Spirulina* blue-green algae (*Arthrospira platensis*) can be used to treat CS and develop anti-TNF therapy. Specifically, the extracts contain C-phycocyanin, a pigment binding protein which can enhance anti-inflammatory activities. It was observed that when these extracts were used to treat LPS-activated macrophages and monocytes, TNF-α secretion levels were reduced by over 70% and 40% respectively [24,26].

In addition to being used as treatment for cytokine storm therapy, other algal bioactive metabolites might have potential in the war against coronavirus.

Marine algae derived sulfated polysaccharides have unique structures which display antiviral effects by obstructing different parts of the viral cycle. It does this by inactivating virions before they can infect or preventing replication inside the infected cell. The bioactive molecules can inhibit the virus at four different stages depending on its properties i) virus attachment, ii) virus penetration, iii) interiorization and viral uncoating, and iv) the viral transcription and translation process [27]. Antiviral properties of algal polysaccharide bioactive metabolites such as carrageenan, fucoidan, ulvan, agar and alginates have been researched against various viruses such as dengue and HIV. Results suggested that there is a possibility of sulphated polysaccharides interfering with the S-protein of SARS-CoV-2 and hence inhibiting viral infection. The negatively charged sulfate polysaccharides interfere with the ionic and electrostatic interaction between the viral surface or receptors and the host cell. Such molecules are not only natural polymers, they are also low cost, biodegradable, non-toxic and biocompatible [25,26].

Polypeptide agents such as lectins which are proteins that reversibly bind to saccharides and display antiviral efficacy. Griffithsin (GRFT) is another promising microalgae derived polypeptide which has shown inhibition of viral entry for cases of HIV, SARS-CoV-1 and MERS-CoV. Other lectins such as cyanovirin-N, scytovirin and agglutinin demonstrate similar properties [25,26].

Lipids from algae sources, namely glycolipids and sulfolipids, exhibit an antiviral effect on enveloped viruses, although less evidently when compared to polysaccharides and proteins [24].

5. Cardiovascular diseases

Atherosclerosis refers to a disease caused by the build-up of plaque in arteries. This plaque is made up of calcium, cholesterol or other substances found in the blood. Hardening of this plaque results in narrowing of the arteries and is responsible for cardiovascular issues. Fucoidan obtained from brown algae is known to be effective in atherosclerosis therapy. Various methods and techniques have been adopted for the utilisation of fucoidans in the treatment of such cardiovascular disorders, following are a few discussed in brief.

5.1 Nitric oxide (NO) and nitric oxide synthase (NOS)

The NO formed by endothelial cells functions as a vasodilator. Thus, keeping NO levels in check seems to be a viable option to treat/prevent cardiovascular disorders.

Decreased NO production observed in cardiovascular disorders are thought to be a consequence of reduced endothelial NOS (eNOS) activity. Studies have concluded that fucoidan causes vascular relaxation through an endothelium-dependent and to some extent NO/cGMP-mediated mechanism, as well as by activating eNOS. Overall fucoidan seems to have increased NO production. Hence these results provide plenty of proof for the use of fucoidan in treating and preventing NO-mediated disorders [28].

5.2 Antithrombotic and anticoagulant effects

Pro-inflammatory cytokines increase the expression of the blood-clotting tissue factor and are also responsible for inhibiting the activity of natural anticoagulants, resulting in increased blood clotting and thrombus formation. The structure activity relationship of fucoidans has been studied immensely, especially in regards to blood coagulation and platelet aggregation.

Fucoidans with higher molecular weight displayed improved anticoagulant effects [29]. When compared to the synthetic drug heparin fucoidan demonstrates a better antithrombotic activity, but a lower anticoagulant activity as well as reduced haemorrhagic risk [30].

Thus, fucoidan is considered a potential medicinal agent with thrombolytic activity owing to its ability to speed up fibrinolysis.

However, the fucoidans derived from different species of brown algae require further preclinical research in regards to their antithrombotic and anticoagulant activity [28].

5.3 Stimulation of revascularization in ischemic or infarcted tissues of the cardiovascular system

Stimulating revascularization or therapeutic angiogenesis, in ischemic zones is an attractive therapeutic strategy. Angiogenic agents with revascularization abilities have gained plenty of attention in recent years. Heparan sulfate proteoglycans (HSPG), are components of the extracellular matrix and then cell surface, which play a vital role in angiogenesis [31]. In this regard, fucoidans have emerged as inducers of vasculogenesis and angiogenesis as they act as competitive inhibitors of HSPG [32].

6. Antibiotic alternatives

In modern medicine, antibiotic resistance is considered one of the foremost problems and challenges in the treatment of infectious diseases. The continuous development and emergence of new and resistant bacterial strains makes finding new ways of treating them more and more difficult. Researchers are focusing on developing substitutes for existing antibiotics to deal with multiple drug resistant (MDR) strains. Algae are an extremely diverse group of organisms which yield a variety of bioactive compounds with anti-bacterial properties, hence containing potential to act as an alternative for already existing antibiotics. Algae are abundant in our ecosystems and can definitely be harnessed to develop novel antibacterial compounds for drugs.

Research conducted has shown that extracts from both freshwater and marine algae contain molecules which display antibacterial properties [33,34]. These extracts are being developed for medical use, mainly due to their lack of toxicity and not killing the human microflora when both consumed or administered directly [35].

A study was conducted with four freshwater microalgae (*Euglena viridis, Chlorella vulgaris, Microcystis aeruginosa* and *Spirulina platensis*) making aqueous, ethanolic and methanolic extracts to test for antibacterial effects. The best responses were shown with the ethanolic extract of *Euglena viridis* against *Vibrio alginolyticus, Vibrio harveyi, Pseudomonas putida* and *Escherichia coli*. Aqueous extracts of *Chlorella vulgaris* also showed antibacterial properties. The crude algal extracts showed better antibacterial activities than some commercial antibiotics (clotrimazole, tetracycline, furazolodone) [33].

Another study with six seaweed species of marine macro algae (*Ulva lactua, Halimedia gracilis, Gracilaria edulis, Hypnea musiformis, Turbinaria conoides,* and *Sargassum myricystum*) had their antibacterial activities tested against bacteria such as *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumonia* and *Enterococcus faecalis*. It was observed that acetonic extracts of all the algae showed most antibacterial activity, with the exception of *Ulva lactua* where the methanolic extract showed most antibacterial activity, presumably due to the bioactive molecules in Ulva being more soluble in methanol [34].

The mechanism of effectiveness for each of the metabolites is unique, with various types of molecules such as polyphenols, polysaccharides, peptides, fatty acids and pigments all showing antibacterial properties when observed in extracts.

Majority of the polyphenols extracts from aquatic sources, marine and freshwater, are algae derived from the Chlorophyceae, Rhodophyceae and Phaephyceae groups. They are mainly secondary metabolites and can be highly diverse due to the linking of multiple hydrozyl groups and benzene

rings. They can vary from simple compounds such as phenolic acids and bromophenols to complex derivatives such as phlorotannin. The antibacterial properties usually occur due to their interactions with multiple sites in the bacteria and disrupting metabolic pathways or surface structural functions [35].

Marine algae mostly have sulfated polysaccharides in their cell walls, a class of compounds which have been harnessed for multiple medicinal purposes as discussed previously. The proposed mechanism by which polysaccharides display antibacterial activity is by binding to the bacterial cell wall membranes and disrupting it, causing disorganization of structure, varied membrane permeability and cell leakage. Fucoidans extracted from brown marine algae *Fucus vesiculosus* were tested against *Escherichia coli, Staphylococcus epidermidis, Staphylococcus aureus,* and *Bacillus licheniformis*. They showed antibacterial activities against all the bacteria, being especially effective against *E. coli* [36].

Algae are a rich source of proteins, having essential amino acids and larger more complex polypeptides with the compositions varying among phyla. Several antimicrobial peptides have been derived from the simple short chain molecules to the larger and more complex proteins that show a wide spectrum of antibacterial activity. Due to their amphiphilic nature, they can interact with both polar and nonpolar cites in the cell membrane, creating pores and causing greater leakage and disruption. Lectins extracted from red algae *Galaxaura marginata* and *Eucheuma serra* showed considerable antibacterial activity against gram negative bacteria [35].

Observations show that the antibacterial potency of free fatty acids (FFA) increases with the level of unsaturation for acids with the same chain length. FFA show antibacterial activity by targeting the cell membrane and inhibiting the electron transport chain and oxidative phosphorylation, preventing nutrient absorption and inhibiting enzyme activity which all together lead to bacterial lysis. Algal extracts concentrated in FFA have shown high antibacterial activity against both gram-positive bacteria such as *Staphylococci* and gram-negative bacteria such as *Vibrio* [35].

Such results show promise when considering algal metabolites as alternatives to existing antibiotics.

7. Conclusion

Algal bioactives have shown a promising future in terms of their therapeutic applications, with their bioactives being widely used in various fields of medicine and therapy. Algal metabolites have seen prominent application in drug delivery systems by complexing with polymers to form drug carriers hence aiding in targeted drug deliveries. When it comes to anticancer and antitumor therapy, algal bioactives have provided a lesser toxic alternative to the widely used chemotherapy, hence their further clinical research has fruitful potential. Antiviral properties of extracts from Spirulina showed immense potential for treatment of cytokine storm in COVID-19 patients, while other peptides and sulfated polysaccharides showed viral inhibition. Bioactives such as fucoidans extracted from brown algae work in a wide variety of ways to treat and even prevent cardiovascular disorders by their antithrombotic/anticoagulant properties and even inducing vasodilation. Emergence of resistant strains of bacteria have resulted in a need for substitutes for current antibiotics and algal metabolites show major potential due to their antibacterial activities. Algal bioactives being less toxic and displaying biodegradability present to us ample therapeutics applications for human health, though further research is required before we can harness its full potential.

Disclosure statement

No potential conflict of interest was reported by the author(s)

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