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Algae Bioactive Constituents and Possible Role During COVID-19 Pandemic (A review)

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Abstract

Nowadays, the use of natural bio-products in pharmaceuticals is gaining popularity as safe alternatives to chemicals and synthetic drugs. Algal products are offering a pure, healthy and sustainable choice for pharmaceutical applications. Algae are photosynthetic microorganisms that can survive in different environmental conditions. Algae have many outstanding properties that make them excellent candidate for use in therapeutics. Algae grow in fresh and marine waters and produce in their cells a wide range of biologically active chemical compounds. These bioactive compounds are offering a great source of highly economic bio-products. The present review discusses the phytochemical and bioactive compounds present in algae biomass and their potent biological activities. The review focuses on the use of alga in therapy and their pharmaceutical applications with special reference to the possible preventive and therapeutic role of algae against COVID-19.

Keywords: Algae, Bioactivity, Therapeutic role, Bio-products, COVID-19, Pharmaceutical

المكونات النشطة بيولوجياً في الطحالب و دورها المحتمل اثناء جائحة COVID-19 (مراجعة)

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الخلاصة

في الوقت الحاضر ، يكتسب استخدام المنتجات الحيوية الطبيعية في المستحضرات الصيدلانية شعبية كبيرة كبدائل آمنة للمواد الكيميائية والادوية المُصنعه. وفي هذا السياق فإن منتجات الطحالب تقدم خيارً طبيعيا وصحيًا ومستدامًا للتطبيقات الصيدلانية. الطحالب عبارة عن كائنات دقيقة تقوم بعملية التمثيل الضوئي يمكنها البقاء في ظروف بيئية مختلفة. تتمتع الطحالب بالعديد من الخصائص المميزه التي تجعلها مرشحًا ممتازًا للاستخدام كعلاج. فنجد ان الطحالب تنمو في المياه العذبة و البحرية و تنتج في خلاياها مجموعة واسعة من المركبات الكيميائية النشطة بيولوجيًا. تقدم هذه المركبات النشطة بيولوجيًا مصدرًا رائعًا للمنتجات الحيوية الاقتصادية. و يناقش هذا البحث مراجعة المركبات الكيميائية النباتية والنشطة بيولوجيًا الموجودة في الكتلة الحيوية للطحالب وأنشطتها البيولوجية. و تركز الدراسةعلى استخدام الطحالب في العلاج وتطبيقاتها الصيدلانية مع إشارة خاصة إلى الدور الوقائي والعلاجي المحتمل للطحالب ضد COVID-19.

الكلمات المفتاحية : الطحالب ؛ النشاط الحيوي؛ الدور العلاجي ؛ المنتجات الحيويه؛ فيروس كورونا؛ المنتجات الصيدلانيه

Introduction

Natural algae products have, for a long time, been commonly explored for human use in food and in medical care [(1)]. Algae are very simple organisms containing chlorophyll, they consist of one single cell or colonies of grouped cells that are essentially not very connected to each other, which makes them of a polyphyletic nature [(2)]. Algae are grouped into two main types namely, macroalgae and microalgae. Microalgae are photosynthetic unicellular microorganisms that are commonly 1 to 400 µm long and are unnoticed for the naked human eye [(3,4)]. Whereas, macroalgae, also known as seaweed are large and multicellular aquatic photosynthetic plant-like organisms[(5)]. Compared to plants, both types of algae have higher growth and biomass productivity and fresh water may not be needed for the cultivation of algae[(6)]. Algae have the ability to be cultivated in all types of water e.g. fresh water, brackish water, seawater and even wastewater[(7)].

It has been extensively proven that both macroalgae and microalgae contain a broad variety of high-value bioactive compounds that can be used as medicinal compounds, nutritious foods and natural pigments [(3)]. Algae are good source of nutrients and bioactive compounds such as antioxidants, fiber, vitamins, minerals, pigments, lectins, steroids, halogenated compounds, proteins, polyunsaturated fatty acids, polysaccharides and other lipids [(2,8–12)]. Algae also contain other bio-products such as carotenoids and amino acids[(13)] . All these bio-products are now being sold for human food and for health use. In the pharmaceutical industry algae are considered as a possible secondary highly bioactive metabolites source that may be useful for developing new pharmaceuticals [(14)].

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Several experimental studies were carried out on the bioactive chemical compounds derived for human gain and welfare from algal biomass. In the present review, a summarized overview of the phytochemical and bioactive compounds present in algae biomass and their potent biological activities is presented. Also, the review points out the pharmaceutical, economic and future prospects for algae role during the present COVID-19 pandemic**.**

Algae

Algae represent a diverse group of largely photosynthetic aquatic organisms[9,15]. Algae can be unicellular, colonial or filamentous, leading to a wide diversity in overall cell morphology [16]. They are present both in aquatic and in fresh water and have a short duplication period, making them one of the most quickly developing species[17]. Algae have diverse methods of assessing and effectively using ambient carbon dioxide and nutrients for biomass production [8,18]. The cell walls of algae are thin, rigid but variable in their conformation and they surround the plasma membranes [16].

In a water body, algal development is a dynamic process characterized by a wide variety of chemical, physical and biological progressions in the interior and it is influenced by a range of environmental factors in the outside. The key factors affecting algal growth have been established as total nitrogen, phosphorus, water temperature, and light strength, and their synergistic effects contribute to algae growth[19].

Algae constitute a group of photosynthetic eukaryotic species[20] that are either autotrophic which use water, light, carbon dioxide and other nutrients to produce their own food or polyphyletic which are large and diverse. Algae on the basis of their morphological characteristics comprise microalgae made up of only one cell or macroalgae (seaweed) that use many different cells to function [21] and they can be identified in freshwater, marine habitats and also on wet rocks [22].

Microalgae

Microalgae are part of the subgroup of algae comprising thousands of types and are in essence photosynthetic. They are categorized as cyanobacteria, rhodophytes, chlorophytes and chromophytes[23]. Microalgae comprises photosynthetic microorganisms that are prokaryotic or eukaryotic, they are single or multicellular in structure [24].

In freshwater and marine environments, microalgae constitute one of the most diverse classes of microorganisms[25]. In taxonomy, microalgae denote eukaryotic microorganisms. However, microalgae include in their widest description prokaryotic cyanobacteria, green algae, diatoms, etc.[26].

The green algae, which belong to phylum *chlorophyta* and contain common generations such as *chlorella*, *dunaliella,* and *haematococcus* are a particularly significant group of microalgae. Another large group is the phylum *Heterokontophyta* diatoms and includes common genera such as *Phaeodactylum* [22,27-29].

Microalgae represent a source of immense bioactive compounds such as antiviral, antibacterial, antifungal and anticancer[30] that can be used for commercial applications. Various microalgae pharmaceutical products have high potential, but their commercialization is still in its initial stages and can be perceived as a portal to the industry worth some billion dollars in the near future [31]. The genetic potential of microalgae for different bioactive agents is amazing. These micro-organisms, as in the pharmaceutical industry, have been shown to be able to manufacture certain compounds in the biotechnological spotlights for use and marketing[32,33].

Macroalgae

Macroalgae, as a fresh and renewable compound source, are currently being researched for both pharmaceutical and nutraceutical applications[25]. They can be categorized according to the presence of distinctive pigments into green algae (*Chlorophyceae*), brown algae (*Phaeophyceae*) and red algae (*Rhodophyceaeae*) [34,35]. According to [36] there are 11017 species of macroalgae on earth and they are distributed as 1901 , 7083 and 2033 for green ,red and brown algae, respectively.

Marine macroalgae have been a significant source of biological and natural compounds including antidiabetic, vitamins, antibacterial and antiviral agents. Macroalgae are renowned for their excellent health, ecological health with a high content of minerals and nutritious fibres [37].

Bioactive constituents of algae

Algae are rich resources for many compounds that are bioactive, including primary and secondary metabolites and that could be used in the pharmaceutical sector as possible candidates of interest [28]. Algae have been proved to be vitamins and vitamin precursors source including ascorbic acid, riboflavin and tocopherol [38]. Algae include a wide variety of medicinal drugs, vaccines, nutritive elements, proteins, which are not otherwise available or which are very expensive to obtain from plant and animal sources[33,39].

Antioxidants

Inflammations and oxidative stress especially in the presence of chronic diseases linked to antioxidant system fragility, are key factors that increase the severity of COVID-19. These data endorse the advice for the supplementation of antioxidants as effective COVID-19 strategies [40].

Antioxidants perform an essential role in the regeneration of damaged cells [41]. In order to avoid these diseases and health issues, antioxidants

terminate the attacks of reactive oxygen species and dramatically controlled oxidative reactions and thus antioxidants are of utmost importance [42]. Antioxidants have a critical role in the prohibition of many disease such as cancer, autoimmune disorders, neurological degeneration and coronary heart. Nowadays, many experts are interested in finding healthy and satisfactory natural antioxidants.

Algae were shown to resist oxidative damages and persist despite exposure to reactive oxygen species and this indicates that algae cells have protective antioxidant defense systems [43].

Natural antioxidants present in many algae are essential bioactive compounds, which play a key role in protecting cells against oxidative damage in various diseases and aging processes. [43].

Sevral algae species showed potential antioxidant activity. Zouaoui and co-authors[44] categorized the algal antioxidants into two groups; (1) water-soluble and (2) fat- soluble. Some of the studies reporting the antioxidant properties of algae species are summarized below.

Anti-oxidant ability has been reported to be correlated with filamentous, green marine algae of *Chaetomorf* species including C. *aerea*, C. *crassa*, C. *linum* and C. *brachygona*. In contrast with other plant species C. *linum* displayed the highest antioxidant potential with a relatively low minimum inhibitory concentration IC_{50} (1.484 ± 0,168 mg mL^{-1}), a highest flavonoid content (18.177 ± 2.238 mg /g as Rutin equivalent) and a relatively low phenolic content (2,895 ± 0,415 mg/g as gallic acid equivalent) [45].

The six brown algae, *Sargassum linearifolium, Sargassum vestitum, Hormosira banksia, Phyllospora comosa, Padina sp., and Sargassum podocanthum* were reported to have antioxidant activity that was correlated to their phenolic compounds content and the six algae were found to contain the potent antioxidant compound "fucoxanthin"[46].

In the four edaphic algae *Vaucheria geminate*, *Pleurochloris pyrenoidosa*, *Botrydiopsis eriensis*, and *Scenedesmus obliquus*, seven phenol compounds were identified (resorcinol, gallic acid, chlorogenic acid, syringic acid, caffeic acid, coumaric acid and ferulic acid). The four species showed high total antioxidant capacity that ranged from 6.66 to 36.33 (mg of Ascorbic acid/g) and also they showed up to 97.37% inhibition for Dimethyl phenyl hydrazyl (DPPH) free radical [28].

The main algal species used to manufacture astaxanthin belongs to the genus *Haematococcus*, but it is also produced by some Chlorella species, such as *Chlamydomonas nivalis*. Astaxanthin is highly important due to its high antioxidant ability and associated health benefits[47].

For its antioxidant qualities, ethanolic and aqueous extracts from seaweed *Polysiphonia* and *Laurencia* have been compared. The content of flavonoids, phenol, and tannins was higher in *Polysiphonia*. Also, *Polysiphonia* displayed higher levels of antioxidant activity relative to *Laurencia* for both ethanol and water extracts [48].

Methanol extracts of the red seaweed, *Chondrococcus hornemannii* and *Spyridia fusiformis* were reported to have high antioxidant activity owing to their phytochemical composition including flavonoids, tannin, alkaloids, saponin and steroids [49].

The methanol extract of blue green algae, *Anabaena sp*. exhibited high antioxidant activity with phenolic content equal to 57.06 gallic acid equivalent (mg/gm) and DPPH radical scavenging activity 48.62±0.29% at 100 mg/ml concentration with an IC_{50} value of 101.81 mg/ml[50].

Antivirals

Viral infections are a big public health concern causing multiple illnesses that endanger health. Many investigations seek to detect novel antivirals in order to monitor and disseminate these contagious conditions[51]. Synthetic antiviral drugs were developed to diminish the virus infections 'complications. On the other hand, serious side effects and development of some resistant mutants of the virus were documented, particularly for long-term antiviral medication[52].

In many studies, researches were driven towards investigating natural sources of antiviral drugs. The antiviral properties of macroalgae have a defensive function against many species of viruses[53,54]. The antiviral activity against certain retroviruses have been found to be compatible with bioactive compounds isolated from microalgae. Steroids and algae-extracted glycolipids have HIV bioactivity[55]. Algae bioactive constituents especially algae derived-polysaccharides have been demonstrated to have potential antiviral activity that could be effective in the treatment of viral infections. In the present review, we are summarizing some of the studies that highlight algae role as antiviral agent[56].

Methanol extract of *Spirulina platensis* isolated from the Nile River in Egypt recorded a pronounced antiviral activity with 50% reduction of viral titer. The observed antiviral activity of *Spirulina* was attributed to its content of sulphoquinovosyl diacylglycerol[57]. Sulphoquinovosyl diacylglycerol is a natural sulpholipid extensive biological activities such as inhibitory effects on DNA polymerase and HIV-reverse transcriptase, P-selectin receptors, the AIDS virus, telomerase, and inflammation/proliferation [58].

The red microalga *Porphyridium* cell-wall sulphated polysaccharide showed remarkable anti-herpes simplex virus type (HSV 1, 2), and Herpes zoster virus type 1 and 2 (HSV 1, 2) Variicella sp (VZV) [59].

Sulfolipids with remarkable antiviral activity against herps simplex virus type1 (HSV-1) were isolated from different marine algal species (*Laurencia popillose, Galaxoura cylindriea, Ulva fasciata, Dilophys fasciola* and *Taonia atomaria*) [60].

The algal extracts of *Spirogyra* showed anti-HSV activity in different phases of the multiplication processes of herpes simplex virus type 1 (HSV 1) and type 2 virus (HSV-2). Alkaloids, essential oils and terpenoids were the major active compounds against HSV found in *Spirogyra spp* ethanolic extract [61].

Aqueous extract from the red macroalga *Laurencia obtusa* inhibited the replication of the viruses: influenza B, A (H3N2) and A (H1N1) [62].

Marine species of Seaweed *Osmundaria obtusiloba* extract revealed high levels Chikungunya virus (CHIKV) infection [63].

The anti-HIV-1 activity of the bioactive compound Fucoidan extracted from two different marine macroalgae *Dictyota bartayesiana* and *Turbinaria* decurrens was proved [63].

Murine leuchemia virus (MuLV), and cell transformation by murine-sarcoma virus (MuSV-124) in cell culture have been substantially inhibited by polysaccharides isolated from the red microalgae *Porphyridium sp.* [64].

Lectins were extracted and purified from *Canavalia brasiliensis* , *C.maritima* , *Dioclea. lasiocarpa*, *D. sclerocarpa* , *Amansia multifida* , *Bryothamniom seaforthii* , *Hypnea musciformis*, *Meristiella echinocarpa* and *Solieria filiformis*. The isolated lectins were efficient for inhibiting 18 different viruses, including HIV and influenza viruses [65].

Antiviral activity against the type 1 Herpes simplex virus, HSV-1 virus and the Rift valley fever virus (RVFV) were investigated and proved for the carragene sulfated polysaccharides isolated from red alga *Acanthophora* and brown alga *Clathratus Hydroclathrus*[66].

COVID-19 disease progression

The emergence of coronavirus (COVID-19) began last November in Wuhan, China, exhibiting pneumonia-like symptoms in patients. By the end of January 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic [67].

Coronaviruses are enveloped viruses that have a single-stranded, positive-sense RNA genome on their surface carrying spike protein. SARS-CoV-2 has high transmissibility and has contributed to a public health epidemic worldwide. Symptoms of COVID-19 range from mild flu-like illness to a potentially fatal syndrome of acute respiratory failure or fulminant pneumonia. Since 2012, more than 800,000 individuals have died as a result of SARS CoV-1 and MERS CoV. In March 2020, the pandemic was declared a pandemic[68].

COVID-19 has an unceasingly rising mortality rate of 0.5-1 percent. An easy way to resist viral infection and reduce fatalities has been to improve immunity. There are currently no drugs and/or vaccines that can help mitigate this viral disease, but spread can be limited by the use of masks and social distancing[69]. The healthcare systems of the entire world are struggling to solve this pandemic. Millions of lives have been disrupted because of mandatory isolation or quarantines[70].

Algae prospective during COVID-19 pandemic

During the current COVID-19 pandemic, scientist all over the world are seeking for exploring new drugs to prevent the infection and to treat the illness but this may take time to verify. In this respect, algae bioactive compounds having antioxidant and antiviral activities could be explored as possible supportive therapy.

Some of the recently tested algal compounds have been promising indications that they are both pharmacologically and commercially efficient antiviral agents and can be used worldwide on a commercial basis to eliminate the infectious pathogen responsible for the COVID-19 pandemic worldwide [71].

According to Pereira and Critchley [72] marine algae species possess large amounts of sulphate polysaccharides of complex structures, which have been shown to inhibit the replication of viruses. The probable antiviral therapeutic antiviral agents against SARS-CoV-2 include molecules such as lectin, carrageen, sulphated polysaccharides, ulvans and fucoidans.

The capacity of algae-based nutraceuticals, in particular *spirulina*, to improve immunity to viral diseases has already been clinically documented. *Spirulina* is considered as a potential bioresource of inhibitory therapeutic-value peptides that may be investigated in the treatment and inflammation of extreme symptoms associated with beta-coronavirus, like COVID-19 [69] .

Conclusion

Presently, most of the researchers are seeking for the development of successful prevention and treatment therapies to prevent infection and cure of COVID-19. Natural bioactive compounds could offer an excellent solution in getting a handle on this pandemic. In this review, we summarized some important studies that discussed the antioxidant, and antiviral properties of Algae-based nutraceuticals and bioactive compounds. In those studies, algae bioactive ingredients were proven to serve as immune-boosting and therapeutic agents. The present review shed the light about the use and pharmaceutical applications of algae in therapy, with particular reference to the possible

preventive and therapeutic functions of algae bioactive compounds against COVID-19.

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