Applications of Green Algae

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Green algae has been always renowned for its potent pharmacological and nutraceutical applications. Besides, anti-cancer, anti-bacterial and anti-oxidant properties, Recently published reports mentioning the potent anti-viral effects of green algae against the deadly virus SARS-CoV-2(COVID-19) has attracted the attention of researchers towards green algae.

Keywords: Marine Chlorophyta, ; SARS-CoV-2, ; Pharmaceuticals, Nutraceuticals, ; Mode of action,

1. Applications of Green Algae

1.1. Chlorophyte as a Spring of Pharmaceuticals and Nutraceuticals

Microalgae represent a diverse and interesting group of microscopic plants that encompasses a relatively high percentage of protein, ranging from 50 to 70% (50% in meat and 15–17% in wheat), 30% in lipids and 40% in glycerol, and a fairly average percentage of carotene (8–14%) and vitamins (B group vitamins, D, E, K, etc.). Microalgae present various physiological and biochemical properties in comparison with other plants and organisms [1]. Moreover, algal organisms represent a rich source of new primary and secondary metabolites biologically active [2]. These metabolites are potential bioactive compounds important for the pharmaceutical industry and may impact it. Seaweeds and their extracts may have various biological activities which include antitumor [3], anti-Alzheimer disease [4], antiprotozoal [5], antiviral [6], antioxidant [7] and cytotoxic action against cell lines in human cancer [8] and some seaweed extracts were also reported to exhibit antimicrobial activity [9][10]. The antimicrobial activity of the macroalgae was determined by the biologically active compounds also containing antibacterial properties, such as cycloeudesmol, lyengaroside A, meroditerpenoid, neoirietetraol, diterpene-benzoate, polybrominated indoles, halogenated sesquiterpene alcohol, lanosol enol ether, diterpene benzoic acids, callophycoic acids, halogenated diterpene-phenols, callophycols and eicosanoids [11]. Elnabris, in a 2013 publication, demonstrated that extracts of marine algae belonging to *Chlorophyta*, namely *Ulva lactuca* and *Enteromorpha compressa* were the most aggressive organisms, and *U. lactuca* proved also to be the most effective [12].

Carotenoids are an effective source of pigmentation; additionally, the antioxidant properties as well as their action in preventing cancer are beneficial for human health, at the skin level having an important role, protecting against UV radiation [13]. Undoubtedly, these compounds are utilized in pharmaceuticals and nutraceuticals. There was a significant increase in skin elasticity and more pronounced skin hydration based on the results of studies on these molecules used in cosmetics. Fucosterol shows strong antioxidant activity, among others, as a terpenoid isolated from *Ecklonia stolonifera*. Fucoxanthin can be an effective ultraviolet protector in cosmetics and sunscreen to delay photoaging. The seaweed tocopherol content was analyzed, revealing that microalgae tend to produce an essential amount of this compound. It is efficient for skin safety to be considered to have an important role in preventing skin and eye pathologies determined by light. Tocopherol is used as a food preservative in many consumer products, as sunscreen in cosmetics, etc. [14]. Carotenoids have a huge prospective for the cure of degenerative disorders, such as macular degeneration and eye cataract [15]. Ketocarotenoid astaxanthin is used in avoiding various human pathological processes like skin UV-mediated photooxidation, inflammation; prostate and mammary carcinogenesis, ulcers and age-related diseases [16]. Green algae have a huge chemical diversity and unique properties based on which they can be used in many ways, like antioxidants, in cosmetics, antibacterial, antiviral, anticancer, etc. Some are discussed below.

1.1.1. Antioxidants

Ulva fasciata Deliles antioxidant properties for the sesquiterpenoids were discovered in green algae when using the free-radical-scavenging assays [17]. The *Ulva lactuca* is enormously acknowledged to have antioxidant properties in flavonoids [18][19]. Info from animal studies unveiled free-radical-scavenging effects of a reticulate hot water extract, due to which hepatic oxidative stress remained reduced [20]. The total content of phenol from the extract of *Cassytha filiformis filiformis* (39.31 ± 0.39 mg of AGE/g extract) was markedly higher ($p < 0.05$) by carrying out *Cassytha filiformis* antioxidant

power ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) and DPPH (2,2′-diphenylpicrylhydrazyl) assays. The extract of *C. filiformis* (IC50 = 3.49 ± 0.01 and 2.18 ± 0.02 mg/mL) was importantly greater ($p < 0.05$), so it is indorsed that the *C. filiformis's* methanol extract is considered as a treasure of secondary metabolites with antioxidant properties [21].

1.1.2. Cosmetics

Green algae are an offering source for cosmetic colorants, phenolic compounds, sterols, vitamins and other therapeutic agents [22]. Some of the bioactive agents (cosmetics) of isolated green algae compounds are used as skin moisturizing and protecting agents, creams with antistretch markings, body ointments, eye balms, face masks, antiaging washing gel, natural sunscreen, body scrubs, face peeling and face salves, firming body liniment, body unguents, purgative gels, fluids, stimulants, shampoos, day and/or night face cream, antielastase, collagen synthesis stimulation, chelating, inducement of collagen making via TGF-β, elastin, proliferation of collagen biosynthesis, anti-photo-aging agents, radical scavengers, colorants, cytoprotective Nrf2-ARE pathway, antiadhesive agents, antiwrinkling, emulsion stabilizers, immune-stimulants, potential for the treatment of histamine-related inflammatory illnesses including atopic dermatitis (AD), inhibition of hyaluronidase, antiallergic, hair growth, adipogenesis inhibitory effect, tyrosinase inhibitors, whitening agents, anticoagulant and topical cosmetic formulations to treat or avoid cellulite, augmented illumination for age spots and skin fall, UV emission defending and comforting, emollient, humectant, oral care, skin conditioning, antifungal and antiseptic, maintaining skin consistency and elasticity, antiacne makeup and many others uses [23].

1.1.3. Antibacterial

A further relevant target of algal extracts comprises oral microbes. *Ulva linza* extracts have antibacterial agents against intermedia *Porphyromonas gingivalis* and *P. intermedia*. Bioactive compounds (stearidonic acid) SA and (gamma-linolenic acid) GLA segregated from *Ulva linza* proved efficient antibacterial activity against *P. intermedia* and *Porphyromonas gingivalis* with MIC values of 39.06 µg/mL and 9.76 µg/mL, respectively [24]. *Ulva lactuca* showed an important antibacterial action against *Escherichia coli* while *Ascophyllum nodosum* was extra perceptive on *Micrococcus luteus* and *Brochothrix thermosphacta. Avrainvillea* sp. consists of bromophenols that pointed out inhibitory activity against both *Bacillus subtilis* and *Staphylococcus aureus*, which were also active against *Pseudomonas aeruginosa* as well as Escherichia coli, *Serratia marcesens* and *Candida albicans* [10]. *Utricularia rigida* composed of fatty acid obtained from Ghar el Melh lagoon can be used for the development of innovative antibacterial ingredients against human marine diseases [25].

1.1.4. Anti-SARS-CoV-2 (COVID-19)

Currently, there is an urge of vaccine which might proceed to immunization against the deadly virus SARS-CoV-2 (COVID-19), but some traits of numerous sea weeds may provide an insight into possible remedies to this global pandemic in the near future. Several marine algae species possess large numbers of hierarchical sulfated polysaccharides which are proved to arrest the replication phase of enveloped viruses such as *Ulvans* [26] and *Caulerpa* [27]. A well-known alkaloidal compound caulerpin was studied In-silico for its antiviral activity against SARS-CoV-2 proteases as a monotherapy and also as a combination therapy with other predicted compounds having efficacy against SARS-CoV-2 such as chloroquine, hydro chloroquine, lopinavir and simeprevir. The results have revealed that caulerpin and its derivatives have shown high binding energies towards SARS-CoV-2 protein receptors as compared to all other predicted drugs. Furthermore, it has been revealed that, by adding different functional groups to the caulerpin structure like vinyl, halogen and NH_2 enhanced the antiviral activity; as well, by adding alkyl groups, are decreased the binding affinities which in turn also decline antiviral activity. In addition, the molecular simulations data showed that the control drug simeprevir and caulerpin derivatives in combination have not shown any fluctuations in the protein and was stable, evidencing that caulerpin and its derivatives can be used as a combinational agent with other drugs, in order to destabilize the SARS-CoV-2 spikes protein [27].

1.1.5. Anticancer

Dichloromethane methanol extracts are derived from two green algae named as *Udotea flabellum* and *U. Conglutinate* chlorophycean algae. The anticancer activity was observed on human melanoma cell line HeLa [28] comparing 22.5 vs. 22.2 µg/mL, respectively. It has been stated that *Udotea flabellum* extracts present antiproliferative activities of the cell lines HeLa, SiHa and KB [28]. *Enteromorpha intestinalis* and *Rhizoclonium riparium*s' methanol extracts with IC50 values 309.048 ± 3.083 µg/mL and 506.081 ± 0.714 µg/mL were proved to be antiproliferative against cervical cancer cell line HeLa [29]. *Enteromopha prolifera* is another genus of green algae that had a suppressive activity with 51.7% for Erhlich's carcinoma inhibition [30]. *Caulerpa*-isolated compounds were assayed against human cancer cell lines A 549 (human cancer carcinoma) and HL-60 (promyelocytic leukemia cells), among isolated compounds, α-tocopherol quinone showed restrained cytotoxicity towards HL-60 and low cytotoxicity towards A-549 [8][31]. Caulerpin's IC50 values were recorded 20 µM against certain cancer cell lines (T47-D, MCF-7, MDA-MB-231, PC3 DU145, HMEC,

HCT116, HT29, LOVO and SW480) but its mechanism of action disclosed that caulerpin obstructs hypoxia-inducible factor 1 (HIF-1) at 10 μM concentration and blocks the induction of HIF-1α protein, an essential oxygen-regulated subunit, under hypoxic circumstances. Caulerpin also has an effect on the migration of tumor cells when the concentration-dependent migration of metastatic MDA-MB-231 cells has been suppressed, with better results being noticed at 30 μM. Operation with Caulerpin in vivo combines with 3-bromopyruvate on xenografts implanted on an athymic nude mouse model carrying SW480. Combination therapy with caulerpin presented fabulous tumor regression. Additional inspection shows that in this combination therapy proliferating cell nuclear antigen (PCNA) and phosphorylated mammalian target phrase rapamycin (p-mTOR) are prevented, showing the important role of adenosine monophosphate-activated protein kinase (AMPK)/mTOR pathway in anticancer therapy. The cultivation of green algae is the best practice to increase the phenol and lipid content and thus improve SI on cancer cells, mostly on the SiHa and Hep-2 cell lines [32]. Through the P13K/Akt pathway, the hot water extract of *Capsosiphon fulvescens*'s polysaccharides determined apoptosis of gastric cancer cells, as well as dimethyl sulfoniopropionate and tertiary sulfonium metabolites, presented anticancer activity in mice with Ehrlich ascites carcinoma [33]. Nigricanosides A is a glycolipid obtained from *Avrainvillea nigricans*, being used in breast cancer cells in mitosis; sesquiterpenoid, known as Caulerpenyne from *Caulerpa taxifolia*, is used in colorectal cancer; sulfated polysaccharide, from *Ulva intestinalis*, is used in reducing tumor mass; sterol, from *Codium fragile*, is used in inducing apoptosis; glycoprotein from *Codium decorticatum* is used to induce apoptosis on MDA-MB-231 breast cancer cells [34]. A novel compound named as 25-hydroperoxy-6β-hydroxycholesta-4,23(E)-dien-3-one, extracted from *Galaxaura marginata*, displayed cytotoxicity against P338 (lymphocytic leukemia cells), A549 (human lung adenocarcinoma epithelial cell lines) and KB (KERATIN-forming tumor cell line HeLa). Cladophoropsis vaucheriaeformis shows tumorigenic behavior against murine lymphoid leukemia L1210 cells [35]. *Chaetomorpha compressa*, the marine green algae, has been proven to be a better anticancer agent against human breast carcinoma cells [36] and shows its antiapoptotic effects against human colon cancer cells HCT-116 [37] In short, green algae are the treasure of bioactive anticancer metabolites.

2. Algae as Nutraceuticals

2.1. Astaxanthin

The *Haematococcus pluvialis* is the key source of Astaxanthin, a powerful natural oxidant having more oxidative properties than vitamin C and E, β carotene, lutein, lycopene and zeaxanthin. Astaxanthin in the human diet can reduce inflammation, oxidative stress and improve the immune system of patients suffering from cardiovascular disease [38]. The involvement of the Natural Algae Astaxanthin Association (NAXA) has an important role in highlighting the advantages and value of astaxanthin. It points out the differences between natural algal astaxanthin and other synthetic sources. Astaxanthin consists of carbon precursors, it contains high lipid-soluble pigment, being basically an antioxidant with rather decreased activity but having good free radical terminator of each carotenoid. Astaxanthins are used as food supplements [39].

2.2. Omega 3 Polyunsaturated Fatty Acids

For the human's body metabolism of PUFA is very important. Chlorophytes are used to extract these important and stable fatty acids. N-6 PUFA is a fatty acid abundant in food. The amount of fatty acids in algae makes them well-known bioactive compounds, very useful in the pharmaceutical industry. Some green algae medicinal applications of green algae are (1) *Enteromorpha*: can be used to treat hemorrhoids, parasitic disease, goiter, coughing and bronchitis; fever reduction capacity and ease pain; (2) *Corallina:* can be used as a pesticide and so on [39]. In short, chlorophytes are extensively used nutritionally as well as pharmaceutically because of their countless benefits. Some unsaturated fatty acids have vital therapeutic properties and benefits for the body. Omega-3 fatty acids lower cholesterol and fat levels in the bloodstream and "cleanse" the blood vessels lining [40]. The use of ω-3 fatty acids as a remedy for heart disease, coronary disease, inflammation, rheumatoid arthritis and immunodeficiency diseases has been revealed by some research [17][41].

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