A Review on Pharmacological Application of Red Algae

Arun Dev Pokharel*, Raju Koneri, Suman Samaddar, Sumitra Poudel, Sudarshan Singh
Karnataka College of Pharmacy, Department of Pharmacology, Bangalore 560064, India
* Author to whom correspondence should be addressed; E-Mail: H2SO4.kingofacids@gmail.com (A.D.P).
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Abstract

The search for natural products with pharmacological properties has led to the discovery of pharmacologically active substances with significant applications in the experimental and therapeutic arenas. Presently, about 25–30% of all active principles used as therapeutic treatments are extracted from natural products. As more than 70% of the world's surface is covered by oceans, the wide diversity of marine organisms offers a rich source of natural products. Among marine organisms, marine algae are rich sources of structurally diverse bioactive compounds with various biological activities. Edible marine algae, sometimes referred as seaweeds, have attracted a special interest as good sources of nutrients and one particular interesting feature is their richness in sulfated polysaccharides (SPs), the uses of which span from food, cosmetic and pharmaceutical industries to microbiology and biotechnology. Marine algae are one of the richest sources of structurally diverse natural products. In recent years, an increasing number of novel compounds have been isolated from marine algae and many of them have been reported to possess interesting biological activities. Therefore, it is clearly documented that, pre-clinical pharmacological research with new marine compounds continued to be extremely active in recent history. Red algae are reported to possess a variety of phytoconstituents including phenols, flavonoids, alkaloids, tannins and terpenoids etc. which in turn account for its enormous pharmacological activities. The constituents obtained from red algae enlarge the chemical library and improve the opportunity to discover new pharmaceutical agents, and interesting novel constituents will still be found in the future. Intensive efforts and obvious progress have been made in recent years and provide evidence that constituents from red algae exhibit diverse biological activities, including antioxidant, antibacterial, anticancer, anti-diabetic, anti-inflammatory, anti-bacterial, anti-viral, anti-HIV, anti-acetylcholinestrase, nephroprotective and hepatoprotective activities.

Keywords: Natural products, Red algae, Bio activities, Marine compounds

1. INTRODUCTION

The search for natural products with pharmacological properties has led to the discovery of pharmacologically active substances with significant applications in the experimental and therapeutic arenas [1-5]. Presently, about 25–30% of all active principles used as therapeutic treatments are extracted from natural products [6]. The plant kingdom is responsible for the majority of chemical diversity reported in the literature to date and has contributed considerably to the research and discovery of new drugs of natural origin, as well as to the supply of therapeutically active compounds [7-11].

Seaweeds as well-balanced, harmless, natural sources with a high degree of bioavailability of trace elements are strongly advised for fast grown children and pregnant women [12]. In contrast to their use as a source of food, marine algae are widely used in the life science as the source of compounds with diverse structural forms and biological activities. Over the years marine algal species offer the biological diversity for sampling in discovery-phase of new drug development [13,14]. Therefore, it is clearly documented that, pre-clinical pharmacological research with new marine compounds continued to be extremely active in recent history [15].

As more than 70% of the world's surface is covered by oceans, the wide diversity of marine organisms offers a rich source of natural products. Marine environment contains a source of functional materials, including polyunsaturated fatty acids (PUFA), polysaccharides, essential minerals and vitamins, antioxidants, enzymes and bioactive peptides [16,17]. Among marine organisms, marine algae are rich sources of structurally diverse bioactive compounds with various biological activities. Recently, their importance as a source of novel bioactive substances is growing rapidly and researchers have revealed that marine algal originated compounds exhibit various biological activities [18,16,19].

Edible marine algae, sometimes referred as seaweeds, have attracted a special interest as good sources of nutrients and one particular interesting feature is their richness in sulfated polysaccharides (SPs), the uses of which span from food, cosmetic and pharmaceutical industries to microbiology and biotechnology [20]. Marine algae are one of the richest sources of structurally diverse natural products. In recent years, an increasing number of novel compounds have been isolated from marine algae and many of them have been reported to possess interesting biological activities [21,22,23].

In this review, we focus on pharmacological applications of marine red algae and present an overview of their bioactivities and potential application in pharmaceutics, since there are only a few reviews in this area.

2. BIOACTIVITIES OF RED ALGAE AND POTENTIAL USE IN MEDICINE

2.1 ANTI CANCER ACTIVITY

Chemotherapy is one of the major therapeutic approaches for cancer treatment, and several naturally obtained anticancer drugs, such as camptothecin and taxol, are used clinically [24]. Regarding to cancer cells resistancy to antitumor drugs, finding new effective anticancer compounds with less side effects has been a field of interest for many scientists. Such studies have been developed in recent years by nanotechnology which represents a new area for health care and biotechnology [25]. There has been many attentions to natural compounds obtained from plants or seaweeds to investigate about their medicinal properties. The antitumor activity was one of the most important activities in marine drugs, and lots of algae and their metabolites have been showed potent cytotoxicity. These metabolites have played an important role in leading to new pharmaceutical compounds from algae for antitumor drugs. Several studies have been done on antitumor activity in the east of Asia. In one study a research group has screened 39 algae from seacoast of China for their possible antitumor activities and they showed that four species of Rhodophyta algae and three species of Phaeophyta exhibited cytotoxic effects against KB and HT-29 cancer cell lines. More than 30 compounds including bromophenols, carotene and steroids were isolated and purified from them and their effects on cancer cell lines have been evaluated separately [26].

Zandi et al studied *Sargassum oligocystum* for its probable anticancer activity against two kinds of human tumor cell lines: Daudi and K562 cell line. Based on their data, sterilizing of the crude extract by filtering is better than autoclaving, so it was concluded that some of its biological constituents are heat sensitive. In the study, the cold-water extract of *Sargassum oligocystum* showed the reasonable activity against tumor cells replication. The most potent antitumor activity has been shown at concentrations 500 µg/ml and 400 µg/ml of the alga extract on Daudi and K562 cell lines, respectively. In the study the effective concentration is more than its counterpart in other studies and it seems that the main reason for this difference is because of using crude extract in the study. Besides, regarding to the number of K562 dead cells after espousing to the different concentration of algal extract they concluded that the cytostatic activity of the tested extract was more regardable comparing to its cytotoxic activity. In conclusion the *Sargassum oligocystum* could be a good candidate for more studies on other cancer cell lines and in vivo antitumor evaluation. It can be a new source as new marine resource for antitumor medicine and to demonstrate that marine algae can be potential candidate sources as antitumor drugs [27].

Priyadarshani et al established a rapid and novel microwave-mediated protocol for extracellular synthesis of metallic silver (Ag) and zinc oxide (ZnO) nanoparticles using the extracts of macro-algae *Gracilaria edulis* (GE) and also examined its anticancer activity against human prostate cancer cell lines (PC3). The formation of silver nanoparticles (GEAgNPs) and zinc oxide nanoparticles (GEZnONPs) in the reaction mixture was determined by ultraviolet-visible spectroscopy. The synthesized Ag and ZnO nanoparticles were characterized by X-ray diffraction, Fourier transform infra-red spectroscopy, energy dispersive X-ray, and field emission scanning electron microscopy. The silver and zinc oxide nanoparticles were spherical and rod shaped, respectively. Cell viability assays were carried out to determine the cytotoxic effects of AgNPs and ZnONPs against PC3 and normal African monkey kidney (VERO) cell line. The inhibitory concentration values were found to be 39.60, 28.55, 53.99 µg/mL and 68.49, 88.05, 71.98 µg/mL against PC3 cells and Vero cells for AgNPs, ZnONPs, and aqueous *G. edulis* extracts, respectively, at 48 h incubation period. As evidenced by acridine orange/ethidium bromide staining, the percentage of the apoptotic bodies was found to be 62 and 70 % for AgNPs and ZnONPs, respectively. The present results strongly suggest that the synthesized ZnONPs showed an effective anticancer activity against PC3 cell lines than AgNPs [28].

Dactylone is representative of a new group of natural cancer-preventive agents. Its chemical structure is closely related to that of sesquiterpenoids extracted from red algae *Laurencia spp.* The effects of dactylone have been studied in many cancer cell lines, including human colon cancer HCT116 cells, and the molecular mechanism underlying these effects was assessed. Dactylone was able to suppress the phenotype expression of various human cancer cell lines and was shown to induce G1-S cell cycle arrest and apoptosis in tumor cells; it decreased Rb protein phosphorylation at Ser795, Ser780, and Ser807/811 sites, and also inhibited the expression of cyclin D3 and cyclin-dependent kinase (Cdk)4. Other studies revealed that inositol hexaphosphate, a dietary constituent found in rice, seems to act in a similar manner as dactylone. Indeed, inositol hexaphosphate has also been reported to decrease Cdk4 and cyclin D1 protein expression levels in addition to the inhibition of Rb phosphorylation at Ser780, Ser807, and Ser811, causing G1 arrest and apoptotic death of human cancers [29].

A sterol fraction extract of *Porphyra dentata*, an edible red alga used as a folk medicine in Asia, was evaluated for its effects on myeloid derived suppressor cells (MDSCs) in 4T1 cancer cells[30]. Previous findings indicated that phytosterols such as β-sitosterol, either alone or in combination with campesterol, may offer protection from various tumors. MDSCs play an important role in tumorigenesis [31-35]. The authors associated the anticancer activity of *Porphyra dentata* with the presence of β-sitosterol and campesterol, which reduced the suppressive activity of MDSCs and consequently decreased tumor size. These two mechanisms

might affect phytosterol-related downregulation of the suppressive activity of MDSCs, which is related to their ROS accumulation and arginase activity [30].

Lins et al investigated the in vitro and in vivo antitumor properties of a sulfated polysaccharide isolated from the seaweed *C. feldmannii* (Cf-PLS). Hematological, biochemical and histopathological analyses were performed in order to evaluate the toxicological aspects related to Cf-PLS treatment. Its effects on the immunological system were also investigated. The Cf-PLS did not show any significant in vitro cytotoxicity at the experimental exposure levels that were used, but showed in vivo antitumor effect. The inhibition rates of sarcoma 180 tumor development were 48.62 and 48.16% at the doses of 10 and 25mgkg−1, respectively. In addition, Cf-PLS was also able to increase the response elicited by 5-fluorouracil (5-FU) from 48.66 to 68.32%. The histopathological analysis of liver and kidney showed that both organs were moderately affected by Cf-PLS-treatment. Neither enzymatic activity of alanine aminotransferase nor urea or creatinine levels were significantly altered. In haematological analysis, leucopeny was observed after 5-FU treatment, but this effect was prevented when the treatment was associated with the Cf-PLS. It was also demonstrated that Cf-PLS acts as an immunomodulatory agent, raising the production of specific antibodies, and increasing the production of OVA-specific antibodies. It also induced a discreet hyperplasia of lymphoid folicules of the white pulp in the spleen of treated mice. In conclusion, Cf-PLS has some anticancer activity that could be associated with its immune stimulating properties [36].

Zandi et al tested different concentration of the aqueous extract from *G. corticata* for probable antitumoral activity on Jurkat and molt4 human lymphoblastic leukemic cell lines. The cells were treated by different concentration of algal extract and the number of viable cells was determined by trypan blue. Also, cytotoxicity of the extract was evaluated by methyl thiazolyl tetrazolium (MTT) assay. The results showed that 9.336 and 9.726 µg/µl of algal extract were the most effective concentrations against Jurkat and molt-4 cells, respectively. The water crude extract of red alga *G. corticata* had significant anticancer activity [37].

2.2 ANTIOXIDANT ACTIVITY

Free radicals attack macromolecules (e.g., membrane lipids, proteins, enzymes, DNA, and RNA) and play a pivotal role in several health disorders such as cancer, diabetes, neurodegenerative and inflammatory diseases. Therefore, antioxidants may have a beneficial effect on human health by preventing free radical damage.

A growing body of results indicates that BPs have potential antioxidant activity, mainly determined by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging method. For example, BPs (2R)-2-(2,3,6-tribromo-4,5-dihydroxybenzyl)-cyclohexanone; 2,3,6-tribromo-4,5-dihydroxybenzylalcohol; 1-(2,3,6-tribromo-4,5-dihydroxybenzyl)pyrrolidin-2-one; 2,3,6-tribromo-4,5-dihydroxybenzylsulfone; 1,2-bis(2,3,6-tribromo-4,5-dihydroxyphenyl)ethane; 6-(2,3,6-tribromo-4,5-dihydroxybenzyl)-2,5-dibromo-3,4- dihydroxybenzyl methyl ether; Bis(2,3,6-tribromo-4,5-dihydroxyphenyl)methane; Bis(2,3,6-tribromo-4,5-dihydroxybenzyl)ether; 2,3,6-tribromo-4,5-dihydroxybenzyl methyl ether; 2,3,6-tribromo-4,5-dihydroxymethylbenzene ; 2,3,6-tribromo-4,5-dihydroxybenzaldehyde isolated from the red algae *Symphyocladia latiuscula*, were reported to possess DPPH radical scavenging activities [38,39].

Grateloupia filicina is an important alga cultivated as a source of food in Korea and Japan. In order to examine its potential antioxidant activity, Athukorala et al. evaluated crude extracts of *G. filicina* for their effect on scavenging of reactive oxygen species (DPPH, DH, H202 and 02-) and inhibition of lipid peroxidation. The activities of these extracts were compared with those of commercial antioxidants such as BHA, BHTand a-tocopherol, the methanolic extract (2 mgimL) of *G. filicina* scavenged 82% of DPPH radicals which is almost three times higher than that of BHT. The same methanolic extract scavenged 65% of superoxide anion which is almost two times higher than that of BHT and cx-tocopherol. In contrast, the extracts in chloroform and carbon tetrachloride inhibited lipid peroxidation more effectively than all commercial antioxidants tested in a Iinoleic acid model system [40].

Palmaria palmata (dulse) is traditionally consumed as a snack food and garnish; but little is known about its potential as a source of antioxidants. Yuan et al extracted 1-butanol soluble fraction from dulse exhibited ºOH scavenging activity ± EDTA (non-site and site-specific activity) in a deoxyribose assay. EC50 concentrations of dulse extract to quench DPPH and ABTS+ free radicals were 12.5 and 29.5 mg/ml. Dulse extract inhibited ($p < 0.05$) conjugated diene production in a linoleic acid emulsion at 24, 48 and 52 h, 38 ºC; and inhibited ($p = 0.044$) thiobarbituric acid reactive substances (TBARS) production at 52 h. One milligram dulse extract exhibited reducing activity = 9.68 lg L-ascorbic acid and total polyphenol content = 10.3 lg gallic acid; the dulse extract did not chelate transition metal ions. The antioxidant activity of the dulse extract was associated with aqueous/alcohol-soluble compounds characterized by phenolic functional groups with reducing activity [41].

Coba et al performed several standard in vitro assays in order to determine the potential antioxidant capabilities of purified aqueous extracts of the mycosporine-like amino acids (MAAs), porphyra-334 plus shinorine (P-334 + SH), isolated from the red alga *Porphyra rosengurttii*, asterina330 plus palythine (AS-330 + PNE), from the red alga *Gelidium corneum*, shinorine (SH), from the red alga *Ahnfeltiopsis devoniensis*, and mycosporine -glycine (MGly), isolated from the marine lichen *Lichina pygmaea*. The scavenging potential of hydrosoluble radicals (ABTS+ decolorization method), the antioxidant activity in lipid medium (β-carotene/

linoleate bleaching method) and the scavenging capacity of superoxide radicals (pyrogallol autooxidation assay) were evaluated. In terms of scavenging of hydrosoluble radicals, the antioxidant activity of all MAAs studied was dose-dependent and it increased with the alkalinity of the medium (pH 6 to 8.5). M-Gly presented the highest activity in all pH tested; at pH 8.5 its IC50 was 8-fold that of L-ascorbic acid (L-ASC) followed by AS-330 + PNE while P-334 + SH and SH showed scarce activity of scavenging of hydrosoluble free radicals. AS-330 + PNE showed high activity for inhibition of β-carotene oxidation relative to vitamin E and superoxide radical scavenging whilst the activity of P-334 +SH and SH were moderate. According to these results, the potential of MAAs in photoprotection can be considered high due to a double function: (1) UV chemical screening with high efficiency for UVB and UVA regions of the solar spectrum, and (2) their antioxidant capacity [42].

2.3 ANTI-DIABETIC ACTIVITY

Diabetes mellitus is a metabolic disorder in which, the body does not produce or properly utilize insulin. In spite of the presence of a series of known antidiabetic medicines in the pharmaceutical market, remedies from marine sources are used with success to treat this disorder. Globally, diabetic cases have exploded in the past two decades at 6% per annum and by the year 2025, 324 million people will be diabetic [43]. Moreover, recently discovered drugs were only ameliorating symptoms and would not cease progression of the disease [44]. According to Sharmanidhi and Garg [45], the synthetic antioxidants for diabetes are suspected to be carcinogenic. Most people in developing countries depend on alternate therapies, including natural resources for their primary health care [46].

Marine algae have been found to have various secondary metabolites. Many marine products that are used for treatment of diabetes throughout the world and there is an increasing demand from patients to use the natural products. Natural sources of drugs from marine algae are used widely, even when their biologically active compounds are unknown, because of their effectiveness, minimal side effects in clinical experience and a relatively low cost. They are one of the less explored sources of pharmacological candidates, and few previous studies have found antidiabetic activities in various marine algae [47-52].

Murugesan et al studied in vitro antidiabetic activity of red seaweed *Portieria hornemannii* (Lyngbye) (Silva) and *Spyridia fusiformis* (Wulfen) using α-amylase and α-glucosidase for inhibitory activity. The methanol extract of *Spyridia fusiformis* revealed at the concentration of 900 µg/mL, α-amylase shows higher activity (84.72 µg/g) than α-glucosidase (94.75 µg/g). The IC50 values wer7e achieved high in *S. fusiformis* at 430 µg/mL in α-amylase and 60 µg/mL in α-glucosidase, nevertheless the IC50 value of α-amylase shows a twofold higher than the α-glucosidase. Results suggest that *P. ornemannii* and *S. fusiformis* could be used as a potent antidiabetic agent [53].

From the experimental data, Mubaasheera et al suggest methanolic extract of *Sargassum polycystum* and *Gracilaria edulis* possess potential antidiabetic activity as it lowers blood glucose level significantly. Methanolic extract of SP and GE also possess significant antihyperlipidemic activity as it lowers serum cholesterol and triglycerides levels, LDL cholesterol and increase HDL cholesterol level. Methanolic extract of SP and GE also showed decrease serum insulin. This suggest that the marine algae possess significant antidiabetic activity and may prove to be good therapeutic agent for managing and treating diabetic mellitus [54].

3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(isopropoxymethyl)benzyl)benzene-1,2-diol (HPN) is a synthetic analogue of 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(ethoxymethyl)benzyl)benzene-1,2-diol (BPN), which is isolated from marine red alga *Rhodomela confervoides* with potent protein tyrosine phosphatase 1B (PTP1B) inhibition (IC_{50} = 0.84 µmol/L). The *in vitro* assay showed that HPN exhibited enhanced inhibitory activity against PTP1B with IC_{50} 0.63 µmol/L and high selectivity against other PTPs (T cell protein tyrosine phosphatase (TCPTP), leucocyte antigen-related tyrosine phosphatase (LAR), Src homology 2-containing protein tyrosine phosphatase-1 (SHP-1) and SHP-2). The results of antihyperglycemic activity using *db*/*db* mouse model demonstrated that HPN significantly decreased plasma glucose ($P < 0.01$) after eight weeks treatment period. HPN lowered serum triglycerides and total cholesterol concentration in a dose-dependent manner. Besides, both of the high and medium dose groups of HPN remarkably decreased HbA1c levels ($P < 0.05$). HPN in the high dose group markedly lowered the insulin level compared to the model group ($P < 0.05$), whereas the effects were less potent than the positive drug rosiglitazone. Western blotting results showed that HPN decreased PTP1B levels in pancreatic tissue. Last but not least, the results of an intraperitoneal glucose tolerance test in Sprague–Dawley rats indicate that HPN have a similar antihyperglycemic activity as rosiglitazone. HPN therefore have potential for development as treatments for Type 2 diabetes [55].

Protein tyrosine phosphatase 1B (PTP1B) plays an important role as a negative regulator in insulin signalling pathways. PTP1B is an effective target for the treatment of type 2 diabetes mellitus. In a study Shi et al, Four bromophenol derivatives from red algae *Rhodomela confervoides*, 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetra-hydroxydiphenyl methane (1), 3-bormo-4,5-bis(2,3-dibromo-4,5-dihydroxybenzyl) pyrocatechol (2), bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (3) and 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxy-methyldiphenylmethane (4) showed significant inhibitory activity against PTP1B (IC_{50} were 2.4, 1.7, 1.5 and 0.84 µmol/L, respectively) as potential therapeutical agents for the treatment of type 2 diabetes mellitus. The anti-hyperglycaemic effects of the ethanol extracts from *R. confervoides* on streptozotocin-induced diabetes (STZ-diabetes) in male Wistar rats fed with high fat diet were investigated. The STZ-diabetic rats treated with medium-dose and high-dose alga extracts showed remarkable reductions in fasting blood glucose (FBG) as compared with the STZ-diabetic control. The results indicate that the *in vivo* anti-

hyperglycemic activity of the *R. confervoides* extracts can be partially attributed to the inhibitory actions against PTP1B of the bromophenol derivatives and that may be of clinical importance in improving the management of type 2 diabetes mellitus [56].

2.4 ANTI-INFLAMMATORY AND ANTINOCICEPTIVE ACTIVITIES

Natural products derived from plants provide an interesting and promising source for isolating and developing therapeutic molecules to fight against various diseases, including inflammatory ones [57]. In this respect, different natural products derived from marine organisms have been reported to exhibit a broad spectrum of pharmacological activity, including anti-inflammatory effects [58,59]. During the process of inflammation, different cell types are recruited, including monocytes that differentiate locally into macrophages. This leads to the regulated production of various pro- and anti-inflammatory mediators including cytokines, such as TNFα, chemokines and inducible enzymes (COX-2 and iNOS) that play critical roles in controlling the inflammatory processes. The expression of most of these proteins is controlled, at least in part, through the activation of a conserved and ubiquitous transcription factor, NF-κB which plays a key role in inflammatory response. Several natural products with anti-inflammatory effects have been shown to target and modulate the NF-κB signaling pathway, including a number of terpenoids [60,61]. Molecules belonging to this family were isolated from different marine organisms including coral, sponge and algae. Algae, particularly red algae, represent a rich source of different secondary metabolites, the majority of which consists of acetogenins, halogenated diterpenes and sesquiterpenes [62-64].

Neorogioltriol is a tricyclic brominated diterpenoid isolated from the organic extract of the red algae *Laurencia glandulifera*. Chatter et al evaluated the anti-inflammatory effects of neorogioltriol both in vivo using carrageenan-induced paw oedema and in vitro on lipopolysaccharide (LPS)-treated Raw264.7 macrophages. The in vivo study demonstrated that the administration of 1 mg/kg of neorogioltriol resulted in the significant reduction of carregeenan-induced rat edema. In vitro, their results show that neorogioltriol treatment decreased the luciferase activity in LPS-stimulated Raw264.7 cells, stably transfected with the NF-κB-dependent luciferase reporter. This effect on NF-κB activation is not mediated through MAPK pathways. The inhibition of NF-κB activity correlates with decreased levels of LPS-induced tumor necrosis factor-alpha (TNFα) present in neorogioltriol treated supernatant cell culture. Further analyses indicated that this product also significantly inhibited the release of nitric oxide and the expression of cyclooxygenase-2 (COX-2) in LPS-stimulated Raw264.7 cells. These latter effects could only be observed for neorogioltriol concentrations below 62.5 µM. To our knowledge, this is the first report describing a molecule derived from Laurencia glandulifera with anti-inflammatory activity both in vivo and in vitro. The effect demonstrated in vitro may be explained by the inhibition of the LPS-induced NF-κB activation and TNFα production. NO release and COX-2 expression may reinforce this effect [65].

Berge et al analysed a sulfoglycolipidic fraction (SF) isolated from the red microalga *Porphyridium cruentum* for fatty acid composition and assayed for ability to inhibit, *in vitro*, the generation of superoxide anion in primed leucocytes and the proliferation of a panel of human cancer cell-lines. Results demonstrated that SF contained large amounts of palmitic acid (26.1%), arachidonic acid (C20: 4ω-6, 36.8%), and eicopentaenoic (C20:5ω-3, 16.6%) acids, and noticeable amounts of 16:1n-9 fatty acid (10.5%). It strongly inhibited both the production of superoxide anion generated by peritoneal leukocytes primed with phorbol myristate acetate (IC50: 29.5 µg/mL), and the growth of human colon adenocarcinoma DLD-1 and to a lesser extent of human breast adenocarcinoma MCF-7, human prostate adenocarcinoma PC-3, and human malignant melanoma M4 Beu cell-lines, and therefore might have a chemopreventive or chemotherapeutic potential, or both. It was found markedly more cytotoxic than sulfoquinovosyldiacyl glycerols from plant used as a standard (STD), due to a stronger ability to inhibit DNA R-polymerase (IC50: 378 µg/mL, vs 1784 µg/mL for STD). After a 48-h continuous treatment, IC50 values for growth inhibition were in the range of 20-46 µg/mL instead of 94 to >250 µg/mL for STD, and those for inhibition of metabolic activity were in the range of 34-87 µg/mL instead of >250 µg/mL for STD. The higher anti-proliferative effect was observed on colon adenocarcinoma DLD-1 cells, and the weaker effect was observed on breast adenocarcinoma MCF-7 [66].

Silva et al evaluated the antinociceptive and anti-inflammatory activities of lectin from the marine alga *Pterocladiella capillacea* lectin (PcL). PcL was purified and tested in classical models of nociception and inflammation. Male Swiss mice received PcL 30 min prior to receiving 0.8% acetic acid (10 ml/10 g, i.p.), 1% formalin (20 ml/intraplantar) or the hot plate test, and were compared to untreated animals or animals pretreated with indomethacin or morphine. PcL (0.9, 8.1 or 72.9 mg/kg, i.v.) significantly reduced the number of writhes (30%, 39%, and 52%, respectively). PcL (72.9 mg/kg, i.v.) also reduced (p0.05) both the first and second phases of the formalin test by 58% and 87%, respectively. However, PcL (72.9 mg/kg) did not present significant antinociceptive effects in the hot plate test when compared to morphine, suggesting that its antinociceptive action occurs via peripheral rather than a central-acting mechanism. It was also observed that leukocyte migration was induced by carrageenan (500 mg/cavity) in male Wistar rats and that PcL (8.1 mg/kg, i.v.) significantly reduced neutrophil migration by 84%, as compared to untreated animals, suggesting inhibition of inflammatory mediators. The data indicated that PcL has peripheral actions with both anti-inflammatory and antinociceptive properties [67].

Bitencourt et al tested the agglutinin from the red marine alga *Hypnea cervicornis* (HCA) in models of nociception and inflammation. The role of carbohydrate-binding sites and the systemic toxicity were assessed. HCA (10−1 , 1, and 10 mg/kg)

administered i.v. to mice inhibited writhes induced by acetic acid and, at 10 mg/kg, inhibited the second phase of the formalin test, but did not alter the response latency in the hot-plate test. HCA (1 mg/kg) administered i.v. to rats reduced carrageenan-induced paw edema at 1, 2, and 3 h after challenge, but not edema induced by dextran. The neutrophil migration induced by both N-formyl-methionyl-leucyl-phenylalanine (fMLP) and carrageenan was inhibited by HCA at 10−1 , 1, and 10 mg/kg. The combination of HCA (1 mg/kg) and its ligand mucin reversed the lectin inhibitory effect on carrageenan-induced neutrophil migration and acetic acid-induced writhes. The i.v. treatment of rats with HCA (1 mg/kg) for 7 days did not affect body mass; liver, kidney or heart wet weight; blood leukocyte counts; urea, creatinine or serum transaminase activity; or macroscopy of the organs examined. In short, *H. cervicornis* agglutinin showed important antinociceptive and anti-inflamatory activity via interaction with the lectin carbohydrate-binding site[68].

Cavalcante-Silva et al investigated the possible antinociceptive and anti-inflammatory activities of a crude methanolic extract of the red alga *Bryothamnion triquetrum* (BT-MeOH) in murine models. Groups of Swiss mice of both sexes (25–30 g) were used throughout the experiments. The potential antinociceptive of BT-MeOH was evaluated by means of the following tests: acetic acid-induced writhing, hot-plate test and glutamate- and formalin-induced nociception. The anti-inflammatory activity of BT-MeOH was investigated using the zymosan A-induced peritonitis test. The tests were conducted using 100 mg/kg (p.o.) BT-MeOH, 33.3 mg/kg (p.o.) dipyrone, 35.7 mg/kg (p.o.) indomethacin and 5.7 mg/kg (s.c.) morphine. The extract and all standard drugs were administered 40 min before the nociceptive/inflammatory stimulus. In the acetic acid-induced writhing test, BT-MeOH and dipyrone inhibited the nociceptive response by 55.9% (22.2 ±2.0 writhings; $p < 0.01$) and 80.9% (9.6 ± 2.1 writhings; $p < 0.01$). In the hot-plate test, BT-MeOH did not increase the latency time of the animals in the time evaluated. In addition, BT-MeOH inhibited glutamate-induced nociception by 50.1%. While BT-MeOH did not inhibit the neurogenic phase in formalin-induced nociception, the inflammatory phase was inhibited by 53.1% (66.8 ± 14.2 s; $p < 0.01$). Indomethacin inhibited the inflammatory phase by 60.2% (56.8 ± 8.7 s; $p < 0.01$). In the zymosan-induced peritonitis test, BT-MeOH inhibited 55.6% (6.6 ± 0.2 ×106 leukocytes/mL; $p < 0.01$) of leukocyte migration, while indomethacin inhibited 78.1% (3.2 ± 0.1 ×106 leukocytes/mL; $p < 0.01$). Based on the results obtained in this study, Cavalcante-Silva et al. concluded that BT-MeOH has peripheral antinociceptive and anti-inflammatory activities [69].

Barbosa et al evaluated the anti-inflammatory effect of a sulphated polysaccharide fraction (PLS) extracted from the alga *Hypnea musciformis* and investigated the possible involvement of the nitric oxide (NO) pathway in this effect.The anti-inflammatory activity of PLS was evaluated using inflammatory agents (carrageenan and dextran) to induce paw oedema and peritonitis in Swiss mice. Samples of paw tissue and peritoneal fluid were removed to determine myeloperoxidase (MPO) activity, NO3/NO2 levels, and interleukin-1b (IL-1b) level. The involvement of NO in the modulation of neutrophil migration in carrageenan-induced paw oedema or peritonitis was also investigated. Key findings Compared with vehicle-treated mice, mice pre-treated with PLS (10 mg/kg) inhibited carrageenan-induced and dextran-induced oedema; it also inhibited total and differential peritoneal leucocyte counts in a model of peritonitis. These PLS effects were reversed by l-arginine treatment and recovered with the administration of a NO synthase blocker (aminoguanidine). Furthermore, PLS reduced the MPO activity, decreased IL-1b levels, and increased NO3/NO2 levels in the peritoneal cavity. By this Barbosa et al concluded PLS reduces the inflammatory response by modulating neutrophil migration, which appeared to be dependent on the NO pathway [70].

Shu et al performed MS/MS analysis of the MeOHGCM6 extracts, revealed the presence of methyl 10-hydroxyphaeophorbide a and 10-hydroxypheophytin a, known chlorophyll proteins and several unidentified molecules. Treatment with 10 μg/ml MeOHGCM6 extract during differentiation of U937 cells significantly inhibited TNF-α response level and TNF-α and IL-6 gene expression. The inhibitory effect was comparable to that of betamethasone. No cytotoxic effects were recorded for cells treated with the 10 μg/ml MeOHGCM6 extract. Rats fed with MeOHGCM6 extract at 500 mg/kg b.w. showed reduced absolute ethanol-induced gastric lesion sizes by > 99% ($p < 0.05$). This protective effect was comparable to that conferred by OMP. The pH of the gastric mucus decreased in dose-dependent manner from 5.51 to 3.82 and there was a significant increase in NP-SH concentrations. Results from the study, suggest that the mass spectrometry standardized methanolic extract of *Gracillaria changii* possesses anti-inflammatory properties[71].

Senevirathne et al prepared enzymatic extracts from *Porphyra tenera* using 4 proteases (Protamex, Neutrase, Flavourzyme, and Alcalase) and 7 carbohydrases (AMG, Celluclast, Dextrozyme, Maltogenase, Termamyl, Promozyme, and Viscozyme), and biological activities of the enzymatic extracts from *P. tenera* were determined as antioxidant, anti-acetylcholinestrase (AChE), and anti-inflammation. The Alcalase and Maltogenase extracts showed higher 1,1- diphenyl-2-picrylhydrozyl (DPPH) scavenging activities compared to the other extracts. At the 2.5 mg/mL, 94.38% (Alacalase extracts), and 80.13% (Maltogenase extracts) scavenging capacities were observed. The Alcalase and Maltogenase extracts were also showed strong reducing power, ferrous ion chelating, and hydrogen peroxide (H2O2) scavenging capacities. In addition, 2 enzymatic extracts effectively protected hydroxyl radical-induced DNA damage. In the case of AChE inhibition, the Flavourzyme (99.32% inhibition) and Viscozyme extracts (82.68% inhibition) were observed. All enzymatic extracts showed no cytotoxicity in RAW264.7 macrophages, and all enzymatic extracts effectively inhibited lipopolysaccharides (LPS)-induced nitric oxide (NO) production in RAW264.7 macrophages. These results suggest that the enzymatic extracts from *P. tenera* would be useful as an ingredient for functional foods [72].

2.4 OTHER ACTIVITIES

Stout et al. isolated three antimalarial meroditerpenes from two Fijian red macroalgae. The absolute stereochemistry of callophycolide, a unique macrolide from *Callophycus serratus*, was determined using a combination of Mosher's ester analysis, circular dichroism analysis with a dimolybdenum tetraacetate complex, and conformational analysis using NOEs. In addition, two known tocopherols, b-tocopherylhydroquinone and d-tocopherylhydroquinone, were isolated from Amphiroa crassa. By oxidizing d-tocopherylhydroquinone to the corresponding d-tocopherylquinone, antimalarial activity against the human malaria parasite *Plasmodium falciparum* was increased by more than 20-fold[73].

Afolayan et al. examined the antiplasmodial organic extracts of the endemic marine red alga *Plocamium cornutum* (Turner) Harvey. Two new and three known halogenated monoterpenes were isolated and their structures determined by standard spectroscopic techniques. The 3,7-dimethyl-3,4-dichloro-octa-1,5,7-triene skeleton is common to all five compounds. Interestingly, compounds bearing the 7-dichloromethyl substituent showed significantly higher antiplasmodial activity toward a chloroquine sensitive strain of *Plasmodium falciparum* [74].

focused on protective effects of an edible red alga, *Laurencia undulata* ethanolic (EtOH) extracts (LU) containing a large amount of polyphenols against OVA-induced murine allergic airway reactions using in vivo histological and cytokine assay. Mice sensitized and challenged with ovalbumin (OVA) showed typical asthmatic reactions as follows: an increase in the number of eosinophil in bronchoalveolar lavage fluid; a marked influx of inflammatory cells into the lung around blood vessels and airways, and airway luminal narrowing; the development of airway hyperresponsiveness; the detection of TNF-a and Th2 cytokines, such as IL-4 and IL-5 in the bronchoalveolar lavage (BAL) fluid; and detection of allergen-specific IgE in the serum. The successive intraperitoneal administration of LU before the last airway OVA-challenge resulted in a significant inhibition of all asthmatic reactions. These results suggest that *L. undulata* polyphenolic extracts possess therapeutic potential for combating bronchial asthma associated with allergic diseases [75].

The gametic, carposporic and tetrasporic reproductive stages from the Mediterranean red alga *Asparagopsis armata* contain peculiar sulfated galactans with galactose:3,6-anhydrogalactose: sulfates molar ratio of 1: 0.01: 1.23, 1: 0.04: 0.47 and 1: 0.01: 1.13, respectively. Haslin et al studied these water-soluble polysaccharides for their in vitro activity against the human immunodeficiency virus (HIV-1). Gametic and tetrasporic galactans inhibit HIV replication at 10 and 8 mg/ml, respectively, as measured by HIV-induced syncitium formation as well as reverse transcriptase activity in cell-free culture supernatant. The carposporic polysaccharide is ineffective, even at 100 mg/ml. The maximal antiviral effect involves the presence of the polysaccharides after or during infection but not before infection. This time of action suggests an inhibition of an early step of HIV infection [76].

Felício et al collected specimens of the red alga *Bostrychia tenella* J. Agardh (Rhodomelaceae, Ceramiales) were collected from the São Paulo coast and submitted to room temperature solvent extraction. The resulting extract was fractionated by partitioning with organic solvent. The n-hexane (BT-H) and dichloromethane (BT-D) fractions showed antiprotozoal potential in biological tests with *Trypanosoma cruzi* and *Leishmania amazonensis* and presented high activity in an antifungal assay with the phytopathogenic fungi *Cladosporium cladosporioides* and *Cladosporium sphaerospermum*. Chromatography methods were used to generate subfractions from BT-H (H01 to H11) and from BT-D (D01 to D19). The subfractions were analyzed by gas chromatography–mass spectrometry (GC/MS), and the substances were identified by retention index (Kovats) and by comparison to databases of commercial mass spectra. The volatile compounds found in marine algae were identified as fatty acids, low molecular mass hydrocarbons, esters and steroids; some of these have been previously described in the literature based on other biological activities. Moreover, uncommon substances, such as neophytadiene were also identified. In a trypanocidal assay, fractions BT-H and BT-D showed IC50 values of 16.8 and 19.1 g/mL, respectively, and were more active than the gentian violet standard (31 g/mL); subfractions H02, H03, D01 and D02 were active against *L. amasonensis*, exhibiting IC50 values of 1.5, 2.7, 4.4, and 4.3 g/mL, respectively (standard amphotericin B: IC50 = 13 g/mL). All fractions showed antifungal potential [77].

Karabay-Yavasoglu et al tested the methanol, dichloromethane, hexane, chloroform and volatile oil extracts of the red alga *Jania rubens in vitro* for their antimicrobial activity (five Gram-positive, four Gram-negative bacteria and *Candida albicans* ATCC 10239). GC-MS analysis of the volatile components of *J. rubens* identified 40 compounds which constituted 77.53% of the total. The volatile components of *J. rubens* consisted of n-docosane (6.35%), n-eicosane (5.77%) and n-tetratriacontane (5.58%) as major components. The methanol and chloroform extracts (4 mg/disc) showed more potent antimicrobial activity than the hexane and dichloromethane extracts and the volatile oil of *J. rubens* [78].

In study by Talyshinsky et al red microalgal polysaccharides significantly inhibited the production of retroviruses (murine leukemia virus- MuLV) and cell transformation by murine sarcoma virus(MuSV-124) in cell culture. The most effective inhibitory effect of these polysaccharides against both cell transformation and virus production was obtained when the polysaccharide was added 2 h before or at the time of infection. Although, addition of the polysaccharide post-infection significantly reduced the number of transformed cells, but its effect was less marked than that obtained when the polysaccharide was added before or at the time of infection. The finding that the inhibition of cell transformation by MuSV-124 was reversible after removal of the polysaccharide

suggested that microalgal polysaccharides inhibited a late step after provirus integration into the host genome. In conclusion, findings could support the possibility that the polysaccharide may affect early steps in the virus replication cycle, such as virus absorption into the host cells, in addition to its effect on a late step after provirus integration [79].

Talarico et al in a study present the chemical composition and antiviral activity against *herpes simple*x virus type 1 (HSV-1) and 2 (HSV-2) of sulfated galactan crude extracts and main fractions obtained from two red seaweeds collected in Brazil, *Gymnogongrus griffithsiae* and *Cryptonemia crenulata*. Most of the eighteen tested products, including homogeneous kappa/iota/nu carrageenan and dl-galactan hybrid, exhibited antiherpetic activity with inhibitory concentration 50% (IC50) values in the range 0.5–5.6g/ml, as determined in a virus plaque reduction assay in Vero cells. The galactans lacked cytotoxic effects and showed a broad spectrum of antiviral activity against HSV-1 and HSV-2. No direct virus inactivation was observed after virion treatment with the galactans. The mode of action of these compounds could be mainly ascribed to an inhibitory effect on virus adsorption. Most importantly, a significant protection against a murine vaginal infection with HSV-2 was afforded by topical treatment with the sulfated galactans [80].

Ahmed et al evaluated the nephroprotective activity of *Eclipta prostrata* hydroalcoholic leaves extracts against gentamicin induced nephrotoxicity in wistar rats for 8 days. Gentamicin induced nephrotoxicity was well manifested by significant increase in renal parameters like serum uric acid, serum urea, serum creatinine, blood urea nitrogen and weight of kidney. The oral administration of hydroalcoholic leaves extracts of *Eclipta prostrata* (250mg/kg and 500mg/kg,p.o) along with gentamicin reversed these altered parameters to normal level when compared with standard cystone (5ml/kg; p.o). The histopathological investigation of kidney was also supported nephroprotective activity of *Eclipta prostrata*. Hence from all the results, it is concluded that *Eclipta prostrata* possess nephroprotective activity due to its antioxidant property [81].

Potassium bromate (KBrO3), an environmental pollutant, is a well-known human carcinogen and a potent nephrotoxic agent. Currently, natural products have built a well-recognized role in the management of many diseases induced by pollutants. As potent natural sources of bioactive compounds, marine algae have been demonstrated to be rich in novel secondary metabolites with a broad range of biological functions. Saad et al treated adult male mice orally for 15 days with KBrO3 (0.5 g/L) associated or not with extract of *Alsidium corallinum*, a red Mediterranean alga. In vitro study demonstrated that algal extract has antioxidant efficacy attributable to the presence of flavonoids and polyphenols. Among these, Liquid chromatography–mass spectrometry analysis showed *A. corallinum* is rich in kaempferol, apigenin, catechin, and quercetin flavonoids. In vivo study showed that supplementation with the alga significantly prevented KBrO3-induced nephrotoxicity as indicated by plasma biomarkers (urea, uric acid, and creatinin levels) and oxidative stress related parameters (malondialdehyde, superoxide dismutase, catalase, glutathione peroxidase, reduced glutathione, vitamin C, hydrogen peroxide, protein oxidation products) in kidney tissue. The corrective effect of *A. corallinum* on KBrO3-induced kidney injury was also supported by molecular and histopathological observations. In conclusion, it was established that the red alga, thanks to its bioactive compounds, effectively counteracts toxic effects of KBrO3 and could be a useful coadjuvant agent for treatment of this pollutant poisonings [82].

3. CONCLUSION

Marine resources have a vast potential to be exploited for the benefits of the mankind. Red algae are reported to possess a variety of phytoconstituents including phenols, flavonoids, alkaloids, tannins and terpenoids etc. which in turn account for its enormous pharmacological activities. The constituents obtained from red algae enlarge the chemical library and improve the opportunity to discover new pharmaceutical agents, and interesting novel constituents will still be found in the future. Intensive efforts and obvious progress have been made in recent years and provide evidence that constituents from red algae exhibit diverse biological activities, including antioxidant, antibacterial, anticancer, anti-diabetic, anti-inflammatory, anti-bacterial, anti-viral, anti-HIV, anti-acetylcholinestrase, nephroprotective and hepatoprotective activities. Further investigations should be carried out to recognize and establish other potential phytoconstituents and pharmacological activities from different red algae.

This review has highlighted the potential pharmacological activities of red algae compounds based on the number of previous studies. With an increasing number of phyto-constituents and their metabolites the red algae hold great promise for novel medicine and industrial application and also found to be rich source of structurally novel and biologically active metabolites.

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