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Review Article

Pharmacological Significance of Marine Seaweed, *Halimeda opuntia*

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Abstract

Nowadays, looking for alternative medicine sources is a hot topic because they are readily available, safe, and, more particularly, come from sustainable sources. Seaweed-based medications are generated in numerous pharmaceutical and biotechnology businesses. Green algae known as *Halimeda opuntia* are particularly prevalent in tropical and subtropical coastal waters that are 1 - 2 meters deep. Numerous research point to this species as a key source of bioactivities and bioactive chemicals, both of which could serve as potential therapeutic targets in the pharmaceutical sector. Based on this hypothesis, a literature review that focused on the pharmacological significance of the seaweed *Halimeda opuntia* was conducted. Here, we report some of the species' drug-targeting effects, including its anticancer, antioxidant, cytotoxic, hypoglycemic, and antibacterial capabilities. This literature review will compel researchers to focus on this species in order to create new medications for human welfare.

Keywords: *Halimeda opuntia; Green Seaweed; Pharmacology; Medicinal Value; Sustainable Drug Development; Bioactive Compounds*

Introduction

Marine environment covers almost about 71% of the earth, which possesses versatile organisms from prokaryotes to eukaryotes and those ranges from primary food chain to tertiary level. Mostly, the primary food producers are green seaweeds and some cyanobacteria related organisms. The ecosystems of the marine origin are much tougher than the terrestrial zone and due to the harsh ecosystem [1], organisms in the marine food chain continuously develops strong defense system in their inner body to sustain [2]. Due to the sustainable growth of the marine organism such as protozoan, metazoan, mollusks, phytoplankton and some other marine grasses and seaweeds, they often produce lots of secondary metabolites, though they also have primary metabolites. These secondary metabolites are of great importance in mankind, especially in health [3]. Many drugs are originated from the marine sources and their efficacy are very high as compared to other terrestrial origin [4].

Peoples are dependent on sea for their food, feed, and drugs as well. Specially, seaweeds are promising in relation to human benefits as they are rich source of protein, carbohydrates, fatty acids, and bioactive compounds. Bioactive compounds are a treasure trove of new therapeutic drugs development, which would have anti-inflammatory, analgesics, hypoglycemic, anti-thrombotic, cytotoxic, anti-microbial, anti-diarrheal, and some other medicinal effects [5]. Seaweeds are rich in minerals, dietary fibers and vitamins [6]. So, they are rich in proximates and minerals [7]. Due to their rich nutritional values, seaweeds can lower the risk of cardiovascular diseases (CVDs); protect against metabolic syndromes, cancer and viral diseases; improve lipid status, reduce inflammations, attenuate weight gain, regulate blood

glucose in type 2 diabetic (T2D) patients and improve the health of bone and digestive tract [8]. However, there is a concern that seaweed consumption may increase exposure to toxic heavy metals such as arsenic, aluminum, cadmium, lead, rubidium, silicon, strontium, and tin although their contribution to total elemental intake does not pose any threat to the consumers [9]. Another possible risk of consuming seaweeds may be the intake of dangerously high concentration of iodine [5]. Nevertheless, considering the health benefits of seaweed consumption, they undoubtedly appear a promising component of the ever-growing market of functional foods or nutraceuticals [10].

Since ancient the time, seaweeds have been employed in herbal therapy [11]. Additionally, they are being investigated as potential sources of bifidobacterial right now [12]. Besides, many cancer therapeutic drugs have been evolved from marine macro- and microalgae. In addition, a recently licensed seaweed-based medication for the treatment of Alzheimer's disease (AD), sodium oligomannate (G V -971), modifies the gut microbiome [13]. Thus, marine algae would have emerging role in drug development.

Bioactive compounds from seaweed

Marine algae are the rich source of bioactive compounds and bioactive peptides that have direct human health benefits [14-19]. The bioactive compounds are found both as primary and secondary metabolites in marine algae [3,20]. Bioactive peptides, polysaccharides (laminarins, fucans, galactans, ulvan, alginates, carrageenan etc.), polyphenols, fatty acids (omega-3 fatty acids such as docosahexaenoic acid, eicosapentaenoic acid etc.), vitamins (both fat soluble vitamins such as vitamin A, vitamin D, vitamin E and water-soluble vitamins such as vitamin C, vitamin B12 etc.), carotenoids, terpenoids etc. have been extracted from seaweeds [2,5]. These compounds have potential diversified pharmaceutical activities [5,10]. Moreover, a database called Seaweed Metabolite Database (SWMD) has been created in order to remain focused on seaweed-derived bioactive chemicals that target the pharmaceutical sector [21].

Halimeda opuntia and its characteristics

Halimeda is a genus of warm temperate to tropical macroalgae whose chloroplasts contain the characteristic photosynthetic pigments of the Chlorophyta along with siphonoxanthin and siphonein, and cell walls are composed of a xylose-based β-1–3 linked xylan. Holdfasts secure their upright, pendent, or sprawling thalli [22]. They have a calcium carbonate endoskeleton that is deposited inside the crevices between the segments formed by medullary filaments [22]. Since this process requires active photosynthesis and the intercellular space to be segregated from the external media by tightly compressed peripheral utricles, the calcification rate in *Halimeda* is enhanced in the light and hindered in the dark [23]. A dense mat of *H. opuntia*, sometimes known as watercress alga, can cover greater areas (about 1 meter) and obscure individual plants. It includes thick, extensively branching clusters of rounded, three-lobed or ribbed leaf-like segments (Figure 1) [22]. It can grow between 10 and 25 cm tall, and its branches are in various planes. It uses its holdfast to cling to hard surfaces. The filament that makes up the holdfast and segments has a diameter of between 0.05 and 0.1 mm and resembles a fungal hypha [24]. *H. opuntia* can be found in all warm seawater on rock about mean sea level down to 2 meters [25]. This species is distributed in tropical and sub-tropical waters, mainly in the Indian Ocean, the Pacific Ocean and also in the Atlantic Ocean [24]. Mostly, it is found in the areas of high predator activity, so that very often it produces a new segment that contains a high concentration of bioactive compounds for their self-defense [26,27].

Bioactive compounds in *Halimeda opuntia*

Generally, the *Halimeda* genus contains various types of bioactive compounds such as alkaloids, halimedatetrasetat, halimedatrial, halitunal, udoteal, rhipocephalin, rhipocephenal, some steroids and polyphenols [14,28]. The chemical composition of the extract contains different bioactive metabolites such as Stigmast-5-en-3-ol, (3β), a phytosterol compound found in plants, was abundant in *H. opuntia*. According to Nazarudin., *et al*. [29], phytosterol functions chemically as a compound with high antioxidant activity and a moderate radical scavenger. The extracts also contains a high concentration of neophytadiene, a member of the sesquiterpenoids class of compounds

[30]. It is said to have powerful antioxidant and anti-inflammatory properties [31]. Meanwhile, 1-dodecanol, 3,7,11-trimethyl found in *H. opuntia* methanolic extract may be responsible for biological effects such as anti-tumor and antimicrobial effects [32]. Cholest-4-en-3-one, a metabolite found in *H. opuntia* methanolic extracts, has been reported to have antitumor activity, decreasing breast cancer cell viability [33]. Hexadecanoic acid is a fatty acid found in high concentrations in *Halimeda* species [29,34]. It has been reported to have antioxidant properties and to be cytotoxic to human colorectal carcinoma cells (HCT-116) [30,35]. Meanwhile, heptadecane and 1-eicosanol have previously been studied for bactericidal activity and have proven to be effective antibacterial agents against a variety of Gram positive and Gram-negative bacteria [36,37].

Figure 1: *Halimeda opuntia species.*

Pharmacological prospects of *Halimeda opuntia*

Based on the literature search, it is known that *H. opuntia* contains potent bioactive compounds that have various pharmacological activities such as antimicrobial, antioxidant, cytotoxic, antileishmanial, antityrosinase, anti-plasmid activities and many more. These bioactivities of *H. opuntia* are due to the presence of phytochemicals in its extracts. Phenolic compounds, flavonoids, alkaloids, steroids, tannins and triterpenes have been detected in its crude extracts [38,39]. A glimpse of pharmacological properties of *Halimeda opuntia* are highlighted below, based on literature tracking and a summary of its pharmacological relevance was mentioned in table 1.

Antioxidant and cytotoxic properties

H. opuntia extracts are known to have antioxidant properties. DPPH scavenging activities have been exhibited by its aqueous extract [40], methanolic extract [41], ethanolic extract [14] and ethyl acetate extract [42]. Polar *H. opuntia* fraction enriched in phenolic compounds was reported to have strong DPPH scavenging activity [43]. One study found that its free phenolic acid (FPA) fractions can increase the expression of superoxide dismutase (SOD) and catalase (CAT) genes and lower the level of thiobarbituric acid reactive substance (TBARS) (a marker of lipid peroxidation) and liver damage in CCl_4-treated rat models [40]. Another study reported the ability of *H. opuntia* methanolic extract to inhibit lipid peroxidation in linoleic acid system [41]. The same study showed its antityrosinase activity [41], which can prevent and treat reactive oxygen species (ROS)-related diseases [44]. Salt of *H. opuntia* may also have strong antioxidant activity [45].

Bioactivity	Extracts/Compounds	Sample collection site	Assays/Methods/ Models	References
Antibacterial Activity against Gram Negative Bacteria				
Escherichia coli	70% ethanolic extracts	Kodiyaghat, South Andaman	Agar well diffusion	[49]
	50% methanolic extracts	Gulf of Lampung	Disc diffusion	[50]
	Ethanolic and methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[51]
	Methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
	Diethyl ether extracts	Mbudya Island, Tanzania	Agar well diffusion	[52]
Serratia marcescens	Dimethylformamide extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
Pseudomonasaeruginosa	Dimethylformamide extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
Salmonella typhi	50% methanolic extracts	Gulf of Lampung	Disc diffusion	[50]
	Ethanolic and methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[51]
Shigella dysenteriae	Ethanolic and methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[51]
Klebsiella pneumoniae	Ethanolic and methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[51]
	Methanolic extract	Jeddah Coast	Agar well diffusion	[41]
Pseudoalteromonas bacteriolytica	Lipophilic extracts	Atlantic islands, Bahamas	Growth inhibition assay (Kubanek., *et al*. 2003)	[55]
Staphylococcus aureus	70% ethanolic extracts	Kodiyaghat, South Andaman	Agar well diffusion	[49]
	Methanolic extracts	Atlantic Coast, Panama	Cylinder plate method	[54]
	Lipid soluble extracts	Magueyes Island, La Parguera	Disc diffusion	[53]
	Dioctyl phthalate or 1,2-Benzenedicarboxylic acid, dioctyl ester		Disc diffusion	[56]
	Isodecyl octyl phthalate or 1,2-Benzene dicarboxylic acid, isodecyl octyl ester		Disc diffusion	[56]
	50% methanolic extracts	Gulf of Lampung	Disc diffusion	[50]
	Methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
	Diethyl ether extracts	Mbudya Island, Tanzania	Agar well diffusion	[52]

Bacillus subtilis	Dioctyl phthalate or 1,2-Benzenedicarboxylic acid, dioctyl ester		Disc diffusion	[56]
	Isodecyl octyl phthalate or 1,2-Benzene dicarboxylic acid, isodecyl octyl ester		Disc diffusion	[56]
	Methanolic extracts	Atlantic Coast, Panama	Cylinder plate method	[54]
	50% methanolic extracts	Gulf of Lampung	Disc diffusion	[50]
	Methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
	Diethyl ether extracts	Mbudya Island, Tanzania	Agar well diffusion	[52]
	Lipid soluble extracts	Magueyes Island, La Parguera	Disc diffusion	[53]
Bacillus cereus	Dimethylformamide extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
Enterococcusaero-genes	Ethanolic and methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[51]
Enterococcus fae-calis	Methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
Antifungal Activity				
Candidaalbicans	Methanolic extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
	Diethyl ether extracts	Mbudya Island, Tanzania	Agar well diffusion	[52]
Candida utilis	Dimethylformamide extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
Saccharomyces cerevisiae	Methanolic and dimethylfor-mamide extracts	Red Sea Coast	Disc diffusion Broth dilution	[46]
Halophytophthora spinosa	Lipophilic and hydrophilic extracts	Atlantic islands, Bahamas	Growth inhibition assay (Kubanek., *et al*. 2003)	[55]
Schizochytriumag-gregatum	Lipophilic extracts	Atlantic islands, Bahamas	Disc diffusion	[55]
Aspergillus flavus	Ethyl acetate extracts	Hurghada coast, Red Sea Coast, Egypt	Sabouraud agar well diffusion	[57]
Aspergillus niger	Ethyl acetate extracts	Hurghada coast, Red Sea Coast, Egypt	Sabouraud agar well diffusion	[57]
Antioxidant activity	Aqueous extract (free phenolic acid extracted with tetrahydrofuran)	Bajo de Santa Ana, Havana City, Cuba	DPPH assay TBARS assay	[40]
	Salt	Pramuka Island Kepulauan Seribu	Cuprac method	[45]
	Methanolic extract	Jeddah Coast	DPPH assay inhibition of lipid peroxidation in linoleic acid system	[41]
	Phenolic acids and their soluble and insoluble esters	Bajo de Santa Ana, Havana, Cuba	DPPH assay β-carotene-linoleic acid system	[43]

Hepatoprotective activity	Free phenolic acid fraction	Bajo de Santa Ana, Havana City, Cuba	CCl_4 treated rats Reverse transcription/ Polymerase chain reaction	[40]
Cytotoxic activity	Methanolic extract	Red Sea Coast	Brine shrimp lethality assay	[46]
	Aqueous extract	Sri Lanka	Brine shrimp lethality assay	[39]
Anti-plasmid activity (on R plasmids of some clinical isolates)	Methanolic extract	Red Sea Coast	Method described by (Deshpande, Dhakephalkar and Kanekar, 2001)	[46]
Antityrosinase activity	Methanolic extract	Jeddah Coast	Modified dopachrome method	[41]
Wound healing activity	Aqueous extract	Coastal areas in Sri Lanka	Scratch would assay using mouse fibroblast (L929) cells	[39]
Interferon β production promoting activity	Methanolic extract	Japan	Poly(I:C) induced human osteosarcoma cell line, MG63	[48]
Antiviral activity against acyclovirresistant HSV-1 and -2	Dichloromethane:methanol (1:1) extract	Southeastern Brazilian Coast	Vero cells	[58]
Antileishmanial activity	80% alcoholic extract	Bajo de Santa Ana	Promastigotes, amastigotes and peritoneal macrophages from BALB/c mice	[59]

***Table 1**: Pharmacological relevance of Halimeda opuntia.*

Methanolic [46] and aqueous [39] extracts of *H. opuntia* may be considerably toxic to brine shrimp nauplii. Halimedatrial, a diterpenoid trialdehyde isolated from *Halimeda* sp., has cytotoxic and antimicrobial activity [26]. 4,9-diacetoxyudoteal, a linear diterpene aldehyde isolated from *H. opuntia*, is toxic to pomacentrid fishes [47]. Another study reported human interferon β production promoting activity of *H. opuntia* methanolic extract [48]. So, *H. opuntia* may be a good source of potent antitumor agents.

Antiviral and antimicrobial properties

Antibacterial activities of *H. opuntia* extracts are well documented. A study reported antibacterial activities of its 70% ethanolic, 70% methanolic and 100% hexane extracts against *E. coli* and *S. aureus* [49]. Another study showed the antibacterial activities of its methanolic extracts against *S. typhi*, *S. aureus*, *B. subtilis* and *E. coli* [50]. In a different study, antibacterial activities of its ethanolic, methanolic, petroleum ether and dimethyl formamide extracts were investigated against *E. coli*, *S. typhi*, *Shigella dysenteriae*, *K. pneumoniae* and *Entero-*

bacter aerogenes [51]. Most extracts, except petroleum ether extract, showed strong antibacterial activities against most of the selected bacteria [51]. In yet another study, antibacterial activities of methanolic, ethanolic, dimethylformamide, hexanic, chloroform, dimethyl sulfoxide and aqueous extracts of *H. opuntia* were assayed against four gram negative (*P. aeruginosa*, *E. coli*, *Proteus vulgaris*, *Serratia marcescens*), six gram positive (*S. aureus*, *Micrococcus luteus*, *Enterococcus faecalis*, *B. subtilis*, *B. cereus*, *B. megaterium*) bacterial species [46]. Methanolic and dimethylformamide extracts showed the highest activity, but no activity was found against *M. luteus*, *B. megaterium* and *P. vulgaris* [46]. Another study demonstrated antibacterial activities of diethyl ether extract of *H. opuntia* against *S. aureus*, *B. subtilis* and *E. coli* [52]. Activities against both *B. subtilis* and *S. aureus* were displayed by its lipid soluble [53] and methanolic extracts [54]. In another study, methanolic extract was found to be very effective against *K. pneumoniae* [41]. A different study reported the lipophilic, but not hydrophilic, constituents of dichloromethane: methanol (1:1) extract of *H. opuntia* to be active against *Pseudoalteromonas bacteriolytica* [55]. Two fatty acids (Dioctyl phthalate and Isodecyl octyl phthalate) isolated from *H. opuntia* have antibacterial activities. Both are active against *B. subtilis* and *S. aureus*, and Isodecyl octyl phthalate is also active against *Streptococcus faecalis* [56].

Antifungal activities of *H. opuntia* extracts have been tested against only a few fungal pathogens. So far, antifungal activities of its extracts have been found against *Candida albicans* [46], *C. utilis* [46], *Saccharomyces cerevisiae* [46], *Halophytophthora spinosa* [55], *Schizochytrium aggregatum* [55], *Aspergillus niger* [57] and *A. flavus* [57]. Its antiviral activity is even less studied. One study found that its dichloromethane: methanol (1:1) extract could be active against acyclovir-resistant Herpes simplex virus-1 and -2 [58]. *H. opuntia* extracts may have antiprotozoal activities. Promising anti-leishmanial activity of its 80% alcoholic extract has been reported [59].

Halimeda opuntia extract also possesses antiviral effect. In a study it was found that *H. opuntia* extract works like MHC class-1 in fish. Study reported that the extract of this species has the ability to activate the MHC class-1, limit the growth of Koi Herpes Virus (KHV) of Cyprinus carpio and also maintains the fish cell harmless [60].

Anticoagulant and wound healing properties

Aqueous extracts of *H. opuntia* may have wound-healing activity [39]. Its methanolic extract can cure R-plasmid from some clinical isolates of *E. coli* [46]. *H. opuntia* can be useful in bioremediation because of its ability to uptake heavy metals [61-63]. It can also improve crop production. Priming seeds of *Triticum aestivum* and *Eruca sativa* with aqueous extract of *H. opuntia*, can mitigate harmful effects under lead stress [64] and cadmium stress [38], respectively. Marine-derived sulfated polysaccharides have anti-coagulant, anti-tumor and anti-viral activities [65].

Endophytes

Endophytic microorganisms residing in marine algae and sponges are the chemical synthesizers, both primary and secondary metabolites, that are beneficial to them as well as the host or symbionts [66] Microorganisms associated with *H. opuntia* can also be a good source of bioactive compounds. The ethyl acetate extract and several compounds extracted from its endophytic fungus *Aspergillus versicolor* contains isorhodoptilometrin-1-methyl ether, emodin, 1-methyl emodin, evariquinone, 7-hydroxyemodin 6,8-methyl ether, siderin, arugosin and variculanol that possesses anticancer (in murine colon 38, human colon HCT-116, human lung H-125, HepG2, murine L1210, human CCRF-CEM, human CFU-GM cell line), antimicrobial activities and inhibitory activities against Hepatitis C virus (HCV) protease [67]. Epiphytic bacteria isolated from *H. opuntia* exhibited significant antibacterial activities [68].

Anticancer agent

Algal bioactive compounds can endanger cytotoxicity by various means such as inhibiting the cancer cell invasion, migration, or metastasis and or controlling the utilization of cell growth metabolites [69]. Several reports suggests that *Halimeda opuntia* possesses anti-

cancer properties due to the presence of lots of bioactive compounds. Studies with methanolic extract of *H. opuntia* in estrogen positive breast cancer cell line (MCF7) and mice fibroblast cell line (3T3) showed increased cytotoxicity with IC_{50} value of 25.14 ± 1.02 and 65.23 ± 0.25 ug/ml respectively. The anticancer activity was also found in the same cell lines with colony formation assay and spheroid formation assay, and it was reported that methanolic extract of *H. opuntia* dramatically abrogated the colony formation and spheroid formation tendency and thus, demonstrated its strong anticancer activity [70]. Besides, methanolic extract of this species also increases apoptosis and necrosis in the MCF7 cancer cell lines [60]. It is known that antioxidant system provides increased defense support to human body for the prevention of cancer [69]. Due to the homeostatic conditions, our body is continuously generating reactive oxygen species (ROS), which are quince away by the active antioxidant system [71-73]. Various natural antioxidants are able to scavenge the ROS and *Halimeda opuntia* also possesses lots of antioxidants such as flavonoids, phenolic compounds, carotenoids, chlorophylls and their derivatives that are the prime bioactive compounds for impeding tumor development [74]. In some animal studies, it was reported that due to the presence of polyphenols from H. opuntia, lots of free radicals were scavenged leading to the inhibition of tumor development [75].

Hawas., *et al*. [67] investigated that the *Halimeda opuntia* endophyte, *Aspergillus versicolor* also possesses anticancer effect due to the presence of siderin, arugosin and variculanol bioactive compounds. These compounds were investigated in two leukemias (murine L1210 and human CCRF-CEM), four solid tumors (murine colon 38, human colon HCT-116, human lung H-125, human liver HEP-G2), as well as human normal cells (CFUGM) using the disk diffusion assay [67].

Hypoglycemic effect

Due to their bioactive secondary metabolites, marine seaweeds have been intensively investigated for their potential to combat diabetes through multiple pathways. Marine algae have been shown to have a hypoglycemic effect in addition to having the ability to reduce diabetic complications in several *in-vitro* and *in-vivo* investigations that have been completed so far.

Alwaleed., *et al*. [76] reported a pancreatoprotective function of *Halimeda opuntia* ethanol extract in alloxan-induced diabetic murine model. *H. opuntia* extract significantly reduced the pre- and post-prandial blood glucose level. It was also observed that the diabetic kidney functions and liver functions were also improved when *H. opuntia* extract was pre-administered to the alloxan-induced model animals. The hematological parameters were also significantly increased in the *H. opuntia* pre-administered groups compared to the negative control and positive control groups. Thus, Alwaleed., *et al*. suggested the *H. opuntia* extract the best extract for use as a preventative medicine (pre-treatment activity) since it improves diabetics by lowering insulin resistance, lowering blood glucose levels, and regenerating damaged beta cells in the pancreas [76].

Conclusion and Future Direction

Due to promising bioactive chemicals, marine seaweeds have recently undergone substantial research for their medicinal properties and *Halimeda opuntia* species would be considered similarly. The purpose of the current study was to evaluate the potential of *Halimeda opuntia* species as a new source for marine pharmaceuticals, which aims to create revolutionary medicines with natural ingredients and reduce the side effects brought on by synthetic substances. Due to the high cost of medications and the poor purchasing power of the people of many nations, access to vital medicines is currently a commodity that only fewer than 50% of the world's population enjoys.

Traditional medicine, which uses natural substances like plants, herbs, and seaweeds to treat diseases and disorders, is this population's first line of defense against health problems. Therefore, it is possible to combine the use of traditional medicine and contemporary treatment, as is currently the case in industrialized and developed nations like United States of America, Japan, Australia, Canada, and France. The lack of sufficient biochemical characterization of the extracts from seaweeds used in traditional medicine, however, might have serious consequences, such as the resurgence of allergies or the assimilation of poisonous substances that can harm our bodies.

Despite the large number of studies that have been done on the compounds and extracts of *Halimeda opuntia* species, more research needs to be done in order to find novel molecules for use in various biotechnological applications, directly and indirectly enhancing human wellbeing.

Author Contribution

MAA- did literature search and wrote the manuscript; TA- searched literature; UC- edited the manuscript; JA- edited the manuscript; MMA- conceived the idea, designed the research, surveyed the literatures, supervised the work, wrote and edited the manuscript.

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Conflict of Interest

Authors have no conflicts of interest to disclose.

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Volume 11 Issue 2 February 2023