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Microalgae as a source of high-value bioactive compounds

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TABLE OF CONTENTS

1. ABSTRACT

Microalgae are one of the oldest microorganisms, that grow in various hostile environments, ranging from deserts to Antarctica. The microalgae sustain life in such harsh environments through generation of secondary metabolites. Microalgae biosynthesize a large number of diverse bioactive metabolites with activities on cancer, neurodegenerative diseases, and infectious diseases. Here, we highlight the bioactive compounds that are isolated from microalgae for the purpose of using them as food, and as chemicals in pharmaceutical industry as new agents with therapeutic benefits.

2. INTRODUCTION

Most algae are autotrophs that live in freshwater and marine environments. They vary from small unicellular microalgae, such as cyanobacteria and diatoms, to large multicellular macroalgae, such as giant kelp (1). Various types of algae have potent capabilities e.g. high levels of EPS secretion potential that help them to survive under different conditions (2). Organisms lacking external defense mechanisms have developed chemical defense strategies, particularly through the production of secondary metabolites with antibiotic or repellent effects (3). Hence, by cultivating them in an adverse environment particularly upon

exposure to abiotic conditions, they can be enriched in a particular bioactive compound (4). Micro and macro-algae, such as diatoms and seaweeds, are enriched with metabolites to fight bacteria and other microbes (5). Antimicrobial agents from the marine environment have been studied with a particular focus to combat current antimicrobial resistance issues. Moreover, introducing enzymes from other organisms via biotechnological means has succeeded in obtaining novel compounds (6). Owing to their potential as a source of industrial, economic and medical/ pharmaceutical interest microalgae have captured the attention of the scientific community (7).

Microalgae ranges from 0.2 to 2 µm (picoplankton) up to filamentous forms with sizes of 100 µm or higher (8). These organisms have the potential for co-production of other molecules such as pigments, proteins, polyunsaturated fatty acids, antioxidants and are gaining attention as therapeutic agents for numerous health disorders and other applications in food, cosmetic, energy and pharmaceutical industries (9-11). Some microalgae are being studied and screened for the detection of active agents like anticancer, anti-inflammatory, antifungal, antibiotics and another pharmaceutical (12, 13). The secondary metabolites from microalgae referred as “High-Value Molecules (HMV)”. Co-utilization of microalgae and fungi have been reported to attain successful removal of pharmaceuticals from wastewater. This occurs mainly via absorption, biotransformation, and degradation, the latter two due to the release of non-specific enzymes (14,15). In this review, a special focus has been given to high-value bioactive compounds isolated from microalgae as new therapeutic agents to advance in the area of biotechnology at large and biomedical in particular. The second part of the review outlines the role of various bioactive compounds of micro-algal origin. The final part focuses on different biological activities including antimicrobial, antiprotozoal, anti-inflammatory, antioxidant, and anticancer to represent their notable potential for biotechnological and biomedical applications.

3. MICROALGAE AS AN INEXHAUSTIBLE SOURCE OF BIOACTIVE COMPOUNDS

The importance of marine organisms as a rich source of structurally diverse and novel bioactive compounds is growing rapidly (16,17). Owing to the presence of valuable compounds like fatty acids, pigments, and other biochemicals, microalgae are considered the potential source for human and animal nutrition (18). However, the low level of these compounds in native microalgae and the difficulty in isolation of pure compounds have limited their production except in few cases such as astaxanthin, and β-carotene, which have been produced at large scale (19). These natural products represent a great structural diversity, belonging to the polyketide synthase (PKS), non-ribosomal polypeptide synthetase (NRPS), as well as hybrid PKS-NRPS structural classes (20). Microalgae have a broad range of application, like in animal feed and nutritional supplements, in cosmetics, pharmaceuticals, bioremediation and water treatment, renewable energy and others (21,22). They also comprise a wide array of biomolecules such as proteins, lipids, vitamins, pigments, that can be harnessed for commercial use in food, cosmetic and pharmaceutical industry (23). Also, the pharmacological activities of various bioactive compounds of microalgal origin such as antioxidant, antitumor, antiangiogenic, hemagglutinating and antiviral have been studied (7, 24, 25).

From the enzymes view point, microalgae proteases have demonstrated superior activities in the natural and alkaline ranges as compared to proteases of higher plant and other organisms (26). The protease inhibitors such as cyanopeptolins, micropenis and oscillate tin from certain cyanobacteria and their selectivity for trypsin/chymotrypsin have also been described (27). In the presence of appropriate metallic ion, microalgae biomass can be used for the production of gold, silver, rhodium and platinum nanoparticles (28,29). The complex environment in their habitat e.g. change in salinity, temperature and nutrient are the contributing factors for producing HVM in microalgae. Consequently, they survive under these conditions by adapting to the new environment and thus produce a significant number of secondary metabolites, which are biologically active and not common in other organisms (30).

4. SECONDARY METABOLITES FROM MICROALGAE

4.1. Carotenoids

Microalgae produce a plethora of high-value carotenoids (31), the most diverse and widespread pigments usually colored yellow, orange, or red (32). They constitute a class of terpenoid pigments, derived from a 40 carbon polyene chain, which is considered as their molecular backbone that provides the carotenoids a unique molecular structure and the associated chemical properties including light-absorption features that are essential for photosynthesis (33). Structurally carotenoids are classified as xanthophylls or oxycarotenoids (astaxanthin (*H. pluvialis*), zeaxanthine (*P. cruentum*), lutein (*C. pyrenoidosa*) and others) and carotenes (α- and β-carotenes (*D. salina*) and lycopene) (34). Carotenes do not have any substituent (or even oxygen) in their structure. They are strict hydrocarbon carotenoids, xanthophylls or oxycarotenoids present –OH groups (hydroxycarotenoids: zeaxanthin from *P. cruentum*, lutein from *C. pyrenoidosa*), =O groups (ketocarotenoid: canthaxanthin from *C. striolata*,

Table 1. Carotenoids from microalgae

Carotenoids	IUPAC Name	Source	Therapeutic Indication	References
β-carotene	β,β-carotene	*D. salina*	Antioxidant, Provitamin A, AMD, Liver fibrosis, anti-inflammatory	(33)(32)
Astaxanthin	3,3′-dihydroxy-β,β-carotene-4,4′-dione	*H. pluvialis*, *C. zofigiensis*, *C. vulgaris*	Antitumoral, anti-oxidant, anti-inflammatory	(35)(19) (41) (32)(10)
Lutein	β,ε-carotene-3,3′-diol	*D. salina*, *C. pyrenoidosa*, *C. protothecoids*	AMD, Atherosclerosis, retinal neural damage	(19) (57)
Zeaxanthin	β,β-carotene-4,4′-diol	*D. salina*, P. cruentum, *C. protothecoids*	Anitoxidant, Maculopathy, cataracts, anti-inflammatory	(57)(35)(19)
Violaxanthin	5,6,5′,6′-diepoxy-5,6,5′,6′-tetrahydro-β,β-carotene-3,3′-diol	*D. tertiolecta*, *C. ellipsoidea*	anti-inflammatory, anti-cancer	(19) (41)(35)
Fucoxanthin	(3S,3′S,5R,5′R,6S,6′R,8′R)-3,5′-dihydroxy-8-oxo-6′,7′-didehydro-5,5′,6,6′,7,8-hexahydro-5,6-epoxy-β,β-caroten-3′-yl acetate	*P. tricornutum*	antioxidant, anti-inflammatory, anti-cancer	(65) (19)

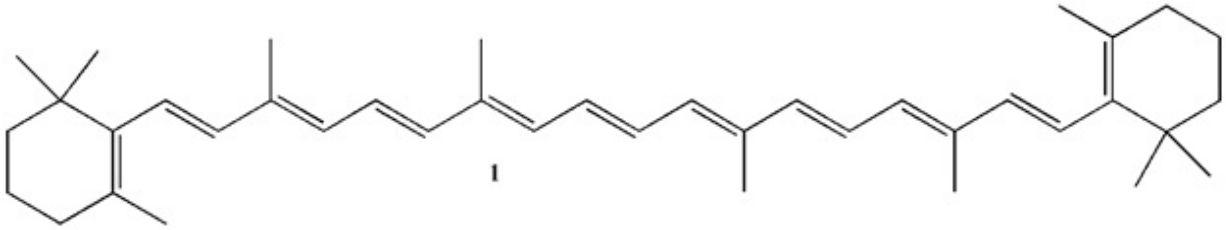

Figure 1. Chemical structure of β-carotene.

echinenone from *B. braunii*, *S. platensis*), or both –OH and =O groups (astaxanthin from *H. pluvialis*) (35). Although there are over 400 carotenoids yet known, those on the market are only a few: β-carotene, astaxanthin and to lesser extent zeaxanthin, lutein, lycopene, fucoxanthin and bixin (32,33). Carotenoids play an important role in the human nutrition and minimize the risk of certain diseases (Table 1), providing provitamin A, preventing cerebrovascular and age-related macular degenerative diseases (36). Moreover, it has been shown that pigments like astaxanthin, β-carotene, lutein, neoxanthin, and zeaxanthin have a scavenging property, while astaxanthin has been claimed to show the highest effect among all carotenoids (34).

4.1.1. β-carotene

The price of micro-algal β-carotene easily reached 700 €/kg, thus have been commercialized (37). While, its synthetic counterpart cannot attain more than half of that amount (33). *Dunaliella*, *Spirulina maxim* and *hematococcus* are the major microalgae species used to produce β-carotene (β, β-carotene) (19,38). β-carotene is one among the leading food colorants, and it has been used in various food and beverage products (39). β-carotene has also been used as a source of vitamin A in animal feed. Provitamin A carotenoids are converted to retinal via catalysis by the intestinal enzyme β-carotene 15,15′-monooxygenase. It has been reported that the uptake of β-carotene-1 (Figure 1) reduces the risk of age-related macular degeneration (AMD) (38,40,41). The natural β-carotene is preferred to the synthetic one in the health market since it is a mixture of cis and trans isomers, the latter has anticancer activity (33).

The demand for β-carotene has increased remarkably as pro-vitamin A (retinol) in multivitamin preparations (33,42). β-carotene can quench singlet oxygen ($^1O_2$*) via electron energy transfer (36,43). It can also prevent eye diseases like cataract and night blindness (32). Moreover, β-carotene blocked the nuclear translocation of the NF-kB p65 protein subunit and inhibited IkBa phosphorylation and degradation to inhibit the inflammatory cytokines *in vivo* and *in vitro* (41). β-carotene has been used to treat disorders such as asthma, cardiovascular and erythropoietic protoporphyria. It has also been used to reduce the risk of several cancers including breast and lung cancer (40,44). Indeed, feeding with both β-carotene-1and supplemental α-tocopherol enhances Th1 cells

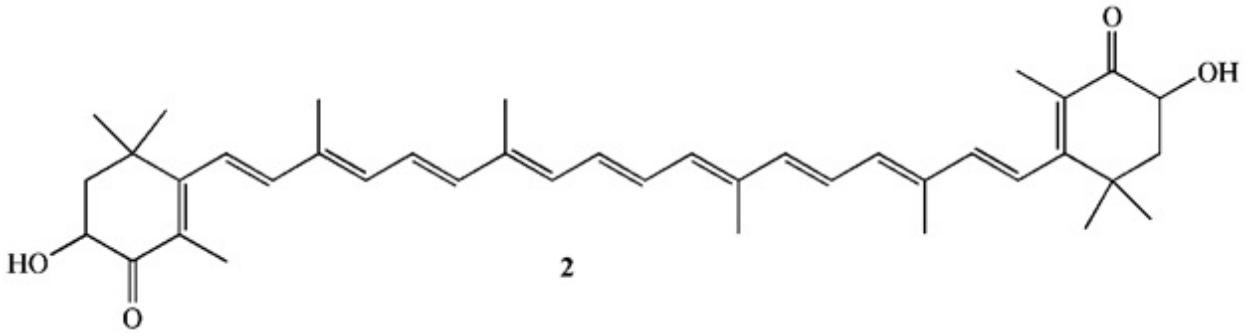

Figure 2. Chemical structure of Astaxanthin.

activity among splenocytes isolated from DO11.1.0 mice. Oral administration of β-carotene-1 to OVA-immunized BALB/c mice led to a lowering of specific IgE and IgG1 titer and caused inhibition of antigen-induced anaphylactic response by decreasing serum histamine level (45).

4.1.2. Astaxanthin

Astaxanthin has a chemical formula of $C_{40}H_{52}O_4$ and a molecular weight of 596.8.6 in geometric cis- and trans-isomers. The trans-isomer is thermodynamically more stable than that of the cis- form (46). It exists in free form and esterified on its one or both -OH groups with different fatty acids such as oleic, palmitic and stearic acids. The natural astaxanthin occurs mainly in esterified form while the synthetic counterpart exists as a free form (47). The main sources of astaxanthin are *Haematococcus Pluvialis, Chlorella zofigiensis, Chlorella vulgaris* and *Chlorococcumsp*. The amounts collected by the green alga *Haematococcus pluvialis* exceed than any other reported source, corresponding up to 4–5% of dry weight (19,41,48,49). The exceptional anti-tumor activity of the red pigment astaxanthin (3,30-dihydroxy-b, bcarotene-4,40-dione) produced by microalgae has attracted considerable attention because it is remarkably potent than β-carotene and other carotenoids (50).

Astaxanthin is responsible for the pinkish appearance of aquatic fish and shrimps. It demonstrates several-fold effective antioxidant activity than β-carotene and vitamin E thus becoming the strongest antioxidant among the carotenoids (32,47). It could also have a synergistic effect with vitamin C that would recharge astaxanthin once it has scavenged ROS via its terminal rings, which appears to be the final scavenger of ROS (51). Dietary Astaxanthin-2 (Figure 2) displays antitumor effects in the post-initiation phase of the carcinogen-induced colon and oral cancer models (50). It has a potential to enhance antibody production, anti-aging, sun-proofing, and anti-inflammatory effects when administered with aspirin. It inhibits low-density lipoprotein (LDL) oxidation and increases high-density lipoprotein (HDL)-cholesterol and adiponectin (32,52). Rao and co-workers (2013) reported that astaxanthin-2 is preferentially absorbed in the liver as compared to β-carotene-1 and lutein-3 from various microalgae. Being a powerful antioxidant astaxanthin increases the level of SOD, catalase, and peroxidase and thus prevent *in vivo* lipid peroxidation (53). Regarding the geometrical isomers of astaxanthin the 3S,3′S isomer was more readily absorbed although it is found in lower concentration in a racemic mixture (35).

4.1.3. Zeaxanthin and Lutein

Microalgae are one of the major sources of naturally occurring zeaxanthin and lutein (54). The main sources of lutein and zeaxanthin include *D. salina*, *C. protothecosis* and *spirulina* (41,55). Two other bio-products (Figure 3), i.e. Lutein-3 and zeaxanthin are also becoming increasingly important in the nutraceutical market (32). The yellow xanthophylls or oxycarotenoid lutein (3R,3′R,6′R-βε-carotene-3,3′-diol) contains two cyclic end groups (one β and one ε-ionone rig). On the other hand, the structurally similar zeaxanthin-4 (β, β-carotene-3,3′-diol) together with lutein accumulates in the central retina (19,56). Epidemiological and intervention trials with lutein and zeaxanthin support a nutrient–health relationship in preventing age-related cataracts and maculopathy (57). In the USA, two lutein-containing products, Aztec Marigold and Tagetes have been recently commercialized.

Lutein-3 is used as a pigment for animal tissue (chicken skin and egg yolks coloring), food, cosmetics, and pharmaceutical products (58), since it has high nutritional value and low toxicity. The anti-inflammatory property against endotoxin-induced uveitis (EIU) via inhibiting Ikβ-α degradation and a subsequent production of pro-inflammatory mediators such as NO, TNF-α, IL-6, PGE2, MCP-1 and MIP-2 has been reported in some studies. Furthermore, oral administration of Zeaxanthin-4 has been found

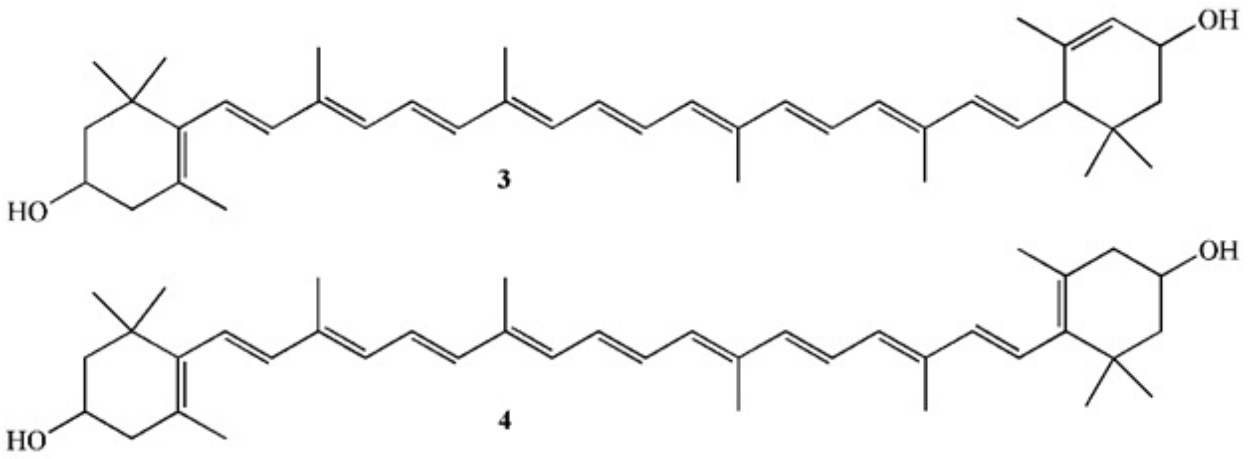

Figure 3. Chemical structures of Lutein (3) and zeaxanthin (4).

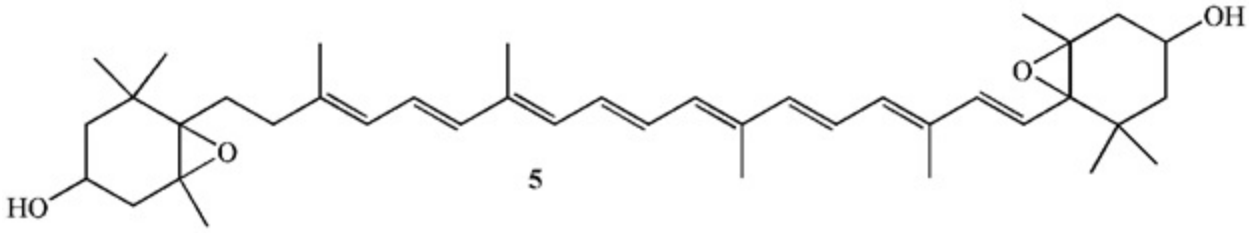

Figure 4. Chemical structure of Violaxanthin.

effective in the management of UVB irradiation induced acute inflammatory responses (41). Both zeaxanthin and lutein are known to play an important function in maintaining a normal visual function (59). Since these organs are susceptible to oxidative damage, lutein and zeaxanthin protect the eye from antioxidant actions, a property which makes them highly valuable chemicals (60). Lutein from *C. vulgaris* was reported to have anti-cancer property against the human colon cancer cell line (HCT-116) and lutein-rich food intake reduced the risk of cancer (61).

4.1.4. Violaxanthin

The chemical structure of violaxanthin-5 (5,6,5′,6′-diepoxy-5,6,5′,6′-tetrahydro-β, β-carotene-3,3′-diol) is illustrated in Figure 4. It is an orange colored natural xanthophyll found in different microalgae. The major sources of this product are *D. tertiolecta* and *C. ellipsoidea* (19). The anti-inflammatory effects of violaxanthine extracted from *C. ellipsoidea* via suppression of the NF-kβ and MAPK pathways suggest that *C. ellipsoidea* has great potential as a candidate for the treatment of inflammatory diseases (41). Soontornchaiboon *et al.* (2012) demonstrated that violaxanthin inhibited the production of NO and PGE2 in a dose-dependent manner in RAW 264.7. cells. The effect of Violaxanthin-5on NO and PGE2 production was consistent with the carotenoids, where β-carotene, lutein, and fucoxanthin were shown to suppress NO production. Moreover, violaxanthin-5reduced PGE2 production and expression of COX-2 at the mRNA and protein level. Therefore, violaxanthin, a non-synthetic natural product, may serve as a safe and effective anti-inflammatory agent, which could be used for therapeutic purposes (62). Violaxanthin exerted a potent anti-proliferative activity on MCF-7 breast cancer cells and induced biochemical changes typical of early apoptosis (63).

4.1.5. Fucoxanthin

Fucoxanthin, a golden-brown-colored carotenoid pigment, was first isolated in 1914 and one of the major carotenoids from marine sources (64). The chemical structure of fucoxanthine-6 ((3S,3’S,5R,5’R,6S,6’R,8’R)-3,5’-dihydroxy-8-oxo-6’,7’-didehydro-5,5’,6,6’,7,8-hexahydro-5,6-epoxy-β, β-carotene-3’-yl acetate) is shown in Figure 5. It is primarily found in various classes of microalgae including bacilophytes, bolidophytes, chrysophytes, silicoflagellates, pinguiophytes and brown microalgae phaehytes (19). Currently, fucoxanthine has received much attention, due to its health benefits, including the

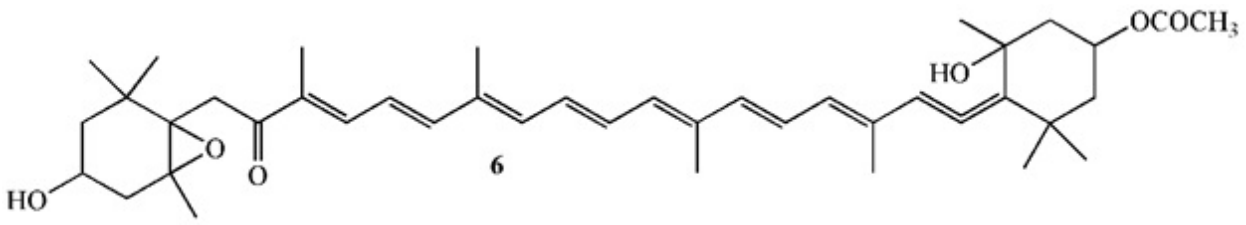

Figure 5. Chemical structure of Fucoxanthine.

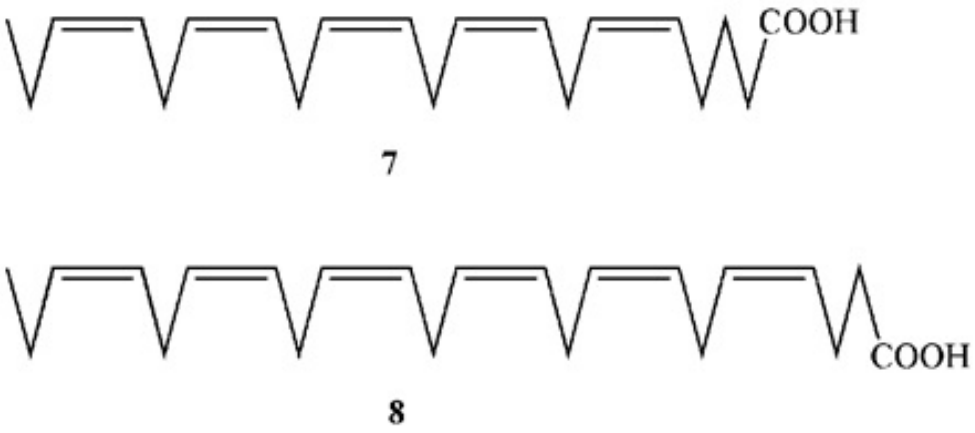

Figure 6. Poly unsaturated fatty acids EPA (7) and DHA (8).

anticancer, anti-obesity, anti-inflammatory, antioxidant, and preventive effect against cerebrovascular diseases (65,66). In addition to increasing the serum level of both HDL and non-HDL cholesterol, fucoxanthine has proved to be nontoxic in a mouse model (65). Several studies indicated that fucoxanthin had exhibited cytotoxicity towards different human cell lines of colon cancer through inducing apoptosis and cell cycle arrest. It had a higher effect on cell viability of colon cancer cell lines (DLD-1, Caco-2, and HT-29) as compared to other carotenoids (61). Moreover, fucoxanthin inhibited a 1,2-dimethylhydrazine induces mouse colon carcinogenesis *in-vivo*. It has also been reported that fucoxanthin could inhibit duodenal and skin carcinogenesis and liver tumorigenesis in mice. The mechanism of action of its anticancer activity in cell cycle arrest, antioxidant action, and apoptosis induction has been reported (65). Fucoxanthin-6 inhibited the NF-kB activation by suppressing Ikβ-adegradation and the nuclear translocation of p50 and p65 proteins in lipopolysaccharide-induced RAW264.7. macrophages. Both fucoxanthin and its metabolite fucoxanthinol demonstrated antioxidant activity as free radical scavengers and quenching singlet oxygen *in-vitro* (65).

4.2. Polyunsaturated Fatty Acids (PUFAs)

PUFAs of more than 18 carbons are not synthesized in animals, and higher plants as the responsible enzymes are not present in these species (18). Although the conventional source of PUFAs is mostly from fish oil, however, the primary PUFAs producers in the oceanic environment are microalgae (67). More recent developments have focused largely on the production of PUFAs, both as nutritional supplements and pharmaceutical agents (68). Virtually all PUFAs originate from primary producers can be modified by bioconversions as they pass up the food chain in a process termed trophic upgrading (69,70). Recent reports suggest that the proportions of essential fatty acids in human diets are correlated with the development of atherosclerosis and coronary heart disease (9). Together with their beneficial effects against cardiovascular system disorders and their protective actions on uncontrolled cellular proliferation, ω-3 PUFAs have been demonstrated to be important physiological components of total brain lipid amount. ω-3 PUFAs plays a crucial role in several neurological functions, such as neurogenesis, neurotransmission, and protection against oxidative stress-induced cerebral damage (11,71,72). It has also been indicated that long-chain N-3 PUFAs, such as docosahexaenoic acid (DHA-8, C22:6n-3) and eicosapentaenoic acid (EPA-7, C20:5n-3) (Figure 6), play important roles in the treatment of many diseases such as cancer, atherosclerosis, rheumatoid arthritis, Alzheimer's, and psoriasis (73). EPA-7 is crucial in human and higher animals as a precursor of a group

of eicosanoids that are important in the development and regulatory physiology. The eicosanoids are hormone-like substances including thromboxane (TX), prostaglandins (PG) and leukotrienes (LT) whereas arachidonic acid (AA, 20:4 N-6) and EPA are precursors of eicosanoid compounds (74,75). EPA-7 and DHA-8 have been reported to decrease circulating levels of CRP, TNF-α, IL-6 and IL-1, and hence may be related to anti-inflammatory processes (71). *C. vulgaris* extracts administered orally to tumor-bearing mice significantly prolonged their survival by enhancing phagocyte production and quality (76). PUFAs have an important role in membrane fluidity, cellular metabolism, transport and as eicosanoid precursors. In the 1980s, the major source of PUFAs was fish oil. Declining fish stocks and contamination has led to use of alternative sources. The market for omega-3-fatty acids was estimated to reach $13 billion in 2011 and expand up to 2016 (77).

4.3. Proteins and Polypeptide

The algal utilization as an alternative nutritional source dates back to the Second World War, after which the consumption of microalgae and seaweeds took center stage to overcome dietary protein deficiency (78). Owing to their high protein content, microalgae are considered potential sources for the production of both elementary proteins and therapeutic peptides and proteins (19). Comprehensive analyses and nutritional studies have demonstrated that these algal proteins are of high quality and comparable to conventional vegetable proteins (79). Due to their high protein content and nutritive value, *Arthrospira*, *Cholorella* and *D. salina* have been utilized in human nutrition diets (80). Spirulina cells have a high nutritional value and high digestibility, due to their richness in various nutrients and high protein content (81). Microalgae synthesize all 20 proteinogenic amino acids and can be unconventional sources of essential amino acids for human nutrition (82). Recombinant DNA and hybridoma technologies made it possible to produce, at large scale, proteins acting as drugs, which are referred to as drugs, biologics, or biopharmaceuticals (BFs) (83). In past, potential vaccine candidates have been produced by viruses and bacteria as well as malaria and other communicable diseases or have been investigated for non-viral diseases (84,85). Anticancer, anti-inflammatory, immunomodulatory, antioxidant, hepatoprotective and neuroprotective activities of phycobiliproteins from marine cyanobacteria and red algae have also been reported (19,86). In comparison to only a few secondary metabolites from ribosomal proteins, a range of cyanobacterial bioactive secondary metabolites is produced via polyketide synthase (PKS) and non-ribosomal peptide synthase (81). The hybrid polyketide–polypeptide structural class of molecules, are characterized by some unique structural features, such as the incorporation of modified amino/hydroxyl acids, heteroaromatic ring systems, as well as extended polyketide-derived units (87). The extended polyketide derived units can be either linear or undergo cyclization to form a common scaffold, like pyrrolidone rings in the Jamaicamides. For example, in the extension of a variety of amino acids a unit of acetate is used, such as Gly, Phe, Pro and Ala (88). Apratoxin A-45 is a mixed peptideepolyketide natural product that comes from a polyketide synthase/nonribosomal peptide synthase pathway of the cyanobacterial secondary metabolite. It is a derivative of the apratoxin family of cytotoxins. This cytotoxin is known for inducing G1-phase cell cycle arrest and apoptosis (89,90).

5. BIOLOGICAL ACTIVITY OF COMPOUNDS FROM MICROALGAE

5.1. Antimicrobial

Despite the fact that microalgae are potential sources of high vale molecules their application as antimicrobials are still in its infancy (91). There is certainly an urgent need for new drugs to treat disease, in particular, new classes of antibiotics to overcome the growing problem of antibiotic resistance in many bacterial pathogens (92). Different natural antimicrobial compounds including fatty acids, indoles, acetogenins, phenols, terpenes and volatile halogenated hydrocarbons have been reported (22). Seaweeds and diatoms have evolved to produce an endogenous system to counter pathogenic bacteria and other microbes, ubiquitous to their environment (5). The metabolites released by these organisms are either bactericidal or halt the bacterial multiplication despite the uncertain mechanism of action they have (91). Treatment for the multi-drug-resistant *S. aureus* has become a challenge except for vancomycin, although the possibility that vancomycin resistance might transfer from vancomycin-resistant *enterococci* to multi-drug resistant *S. aureus* has been extremely worrying (93). Some studies reported that polysaccharides released to culture medium by some microalgae had been confirmed to have antiviral activity against various viral species, either mammalian or others (24). Extracellular sulfated polysaccharides A1 and A2 were isolated and purified from *C. polykrikoides*, marine microalgae. A1 and A2 inhibit the cytopathic effects of influenza virus types A and B grown on MDCK cells, and RSV types A and B has grown on Hep-2 cells (94).

Novel antimicrobial agents from the microalgal source are shown in Figure 7). Long-chain fatty acids with antibacterial activity in the green microalgae *P. nureskis* is reported to have considerable inhibitory effect against *C. jejuni*, *E. coli* and *S. enteric* (5). Pane *et al.*, reported that extracts from *D. tertiolecta*and *P. subcapitatacan* yield compound provided with antimicrobial activity useful

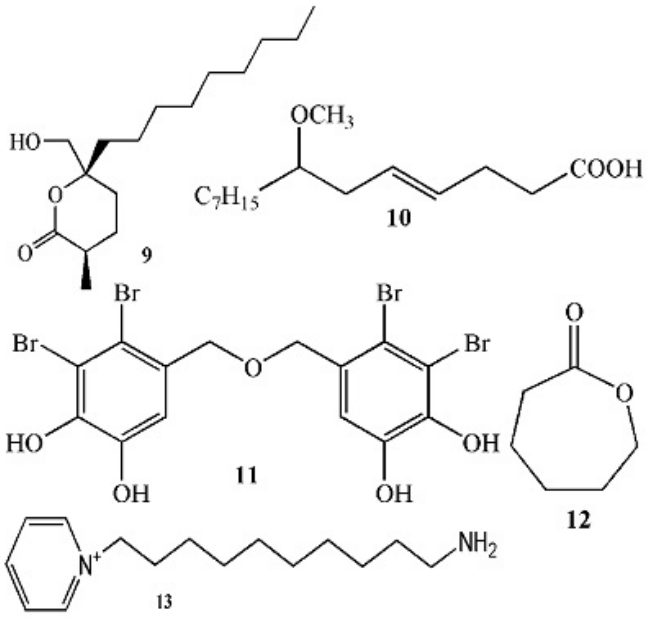

Figure 7. Antimicrobial compounds from natural products of the microalgal source.

for the treatment of otolaryngological diseases due to bacterial agents (95). In another study, it was reported that the c-lactone malyngolide-9 an antibiotic effective against *M. smegmatis* and *S. pyogenes* was isolated from the dichloromethane extract of a shallow-water variety of the blue–green algae *L. majuscula*. The major antimicrobial constituents of Puerto Rican specimens of the blue-green *Lyngbya majuscula* are the elemental sulfur and (-) -(4E,7S)-7 methoxytetradec-4-enoic acid-10 (96). In one study it was reported that bis(2,3-dibromo-4,5-dihydroxybenzyl) ether-11 demonstrated antibacterial activity against *S. aureus* (MIC=10µg/ml), *P. aeruginosa* and *S. epidermis*, among five bromophenols isolated from *R. confervoids* (97). Caprolactones-12 are new antibiotics isolated from *Streptomyces sp*. showing moderate phytotoxicity and promising activity against cancer cells with concomitant low general cytotoxicity (98). Pyridinium-13 is an antibiotic isolated from *Amycolatopsis alba* (98).

5.2. Antiprotozoal agents

Marine cyanobacteria are proving a valuable source of antimalarial compounds of diverse structure types, including alkylated phenols, alkaloids, and cyclic and linear peptides. Of these, gallinamide A-18 most closely resembles the structures of the linear peptides dolastatin 10 and 15, which has been shown to exhibit both antimalarial and mammalian cell anti-proliferative effects. By contrast, gallinamide A is a reasonably effective antimalarial whose relative potency against parasites (8-10 µM) versus mammalian cells (generally>17µM) suggests that this structural framework could be an attractive foundation for further SAR investigations (99). Recently, new bioactive compounds called viridamide A-14 and B-15 were isolated from the marine cyanobacterial natural product. They are linear lipopeptides with novel terminal proline methyl ester, a terminal acetylene group, and a 5-methoxydec-9-ynoic acid moiety. It was reported that viridamide A has anti-leishmanial activity with an IC_{50} of 1.5. µM and anti-trypanosomal activity with an IC_{50} of 1.1. µM (100). Likewise, bioassay-guides isolation efforts produced several unique linear peptides with activity, such as the lipoprotein gallinamide A-18 with anti-malarial activity, almiramide A-17 and dragonamide E-16 with anti-leishmanial activity (Figure 8) (101). One of the most potent marine cyanobacterial antimalarial compounds reported to date is symplostatin 4-19 with an EC_{50} value of 74 nM when tested againstPlasmodium falciparum strain 3D7(89). The AgCl-NPs derived from a green microalgal species *C. vulgaris* was a promising regarding anti-proliferative effect against Gram-negative and Gram-positive bacteria. However, a further set of antimicrobial susceptibility testing, including minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs), should be performed to prove theAgCl-NPs antibacterial performance (28).

5.3. Anti-Inflammatory Activity

Inflammation is a vital process in acute diseases, and it is essential to identify and destroy invading pathogens in the host. However, if it occurs as chronic and subclinical condition and if the process is

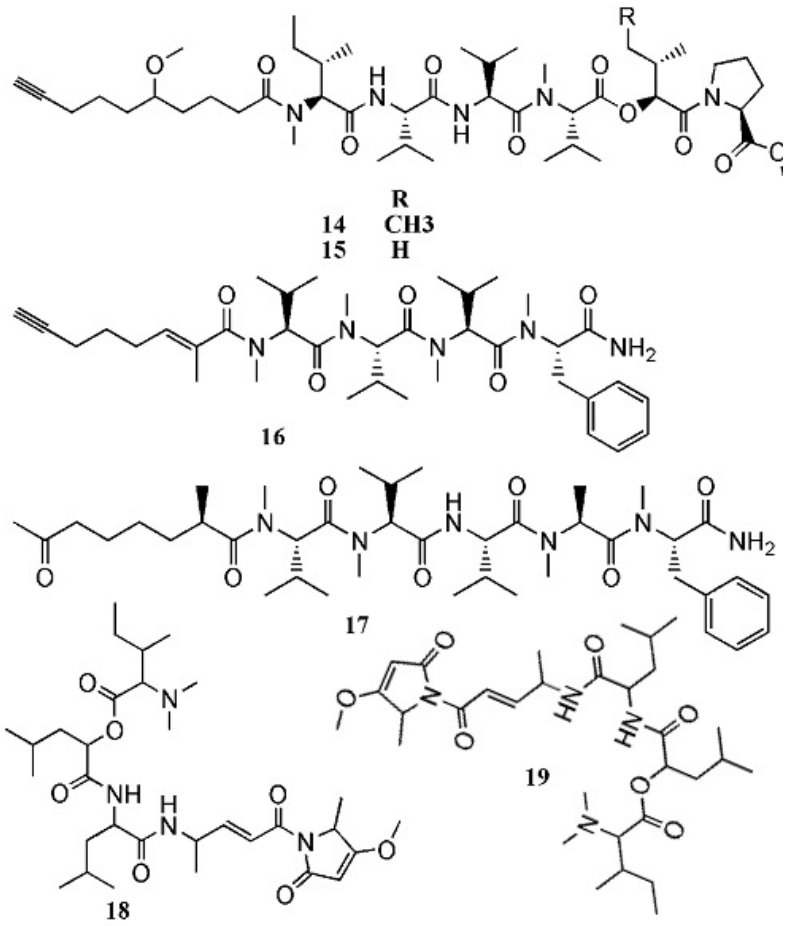

Figure 8. Structure of antiprotozoal compounds of microalgal origin.

not regulated over a long period, the activated immune system can damage host tissues and up-regulate chronic disease states like cardiovascular disease, Alzheimer's disease, inflammatory bowl, disease and obesity (102). Many bioactive compounds isolated from marine life have shown potent and mechanistically intriguing anti-inflammatory activities, and contribution of marine cyanobacteria to this class of compounds is recognizable (for instance, anti-inflammatory bis-bromoindoles from *Rivularia sp.*) (101). Micro-algal phytosterols and their secondary metabolites are promising potential anti-inflammatory agents and the synergistic effect should always take into consideration when optimizing the functionality (103). Microalgae such as *Phaeodactylum, Poryphyridium,* and *C. stigmatophora* produces polysaccharides with pharmacological activity, such as anti-inflammatory and immunomodulating activities (24). The anti-inflammatory activities of PUFAs have been indicated in various *in-vivo* skin models (19). Recently, several metabolites from marine cyanobacteria were tested by nitric oxide (NO) inhibition assay in a mouse RAW macrophage cell line. It was discovered that several malyngamides were quite potent inhibitors, particularly those in the F series, malyngamide F acetate-20 (Figure 9). Other malyngamides like malyngamide-21 also showed anti-inflammatory activity (101).

5.4. Antioxidant

The demand for a safe and powerful antioxidant from a natural product is growing worldwide. This is because the need to minimize oxidative damage to living cells and prevent deterioration in commercialized products such as food, pharmaceuticals or cosmetics is increasing (23,104). Oxidative damage due to ROS such as hydroxyl radical (HO•), superoxide anion and hydrogen peroxide (H_2O_2) could induce atherosclerosis, cataracts, muscular dystrophy, rheumatoid arthritis, neurological damage, cancer and aging (105). Owing to the the health concern and risks caused by synthetic antioxidants such as butylated hydroxytoluene (BHT) and propyl gallate (PG), antioxidants from the natural product are urgently required (103). The photoautotrophs are highly exposed to oxidative and radical stresses in their natural habitats, to overcome the oxidative stress (24,106). Antioxidant molecules from microalgae,

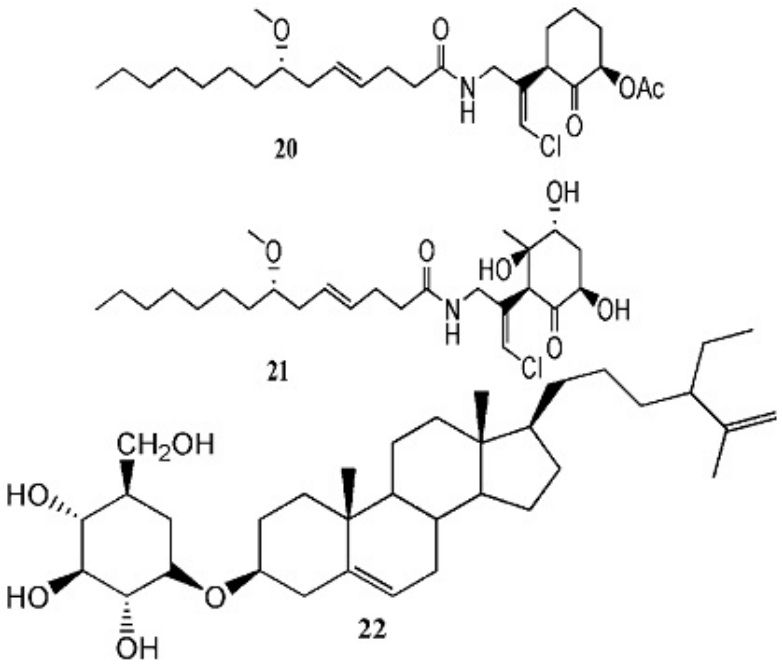

Figure 9. Antiinflammatory compounds malyngamide F acetate (20), malyngamide (21) and 3-0-b-D-glucopyranosy-lstigmasta-5,25-diene (22).

especially carotenoids, phenolic compounds, fatty acids, tocopherol, flavonoids, and alkaloids play a major role in the control of the oxidative process (23,43,51,107). Dermacozines A-23 to G-29are new the oxidized and reduced phenazine-type pigments of dermacoccus isolated from the sediments of the Challenger Deep (10898 m) of the Mariana Trench. Dermacozines F-28 and G-29exhibited moderate cytotoxic activity against leukemia cell line K562 with IC50values of 9 and 7 M, respectively while the highest radical scavenger activity was observed in dermacozine C 25with an IC50value of 8.4. M (98). Also, eckol-30, dieckol-31, phlorofucofuroeckol A-32and 8,8'–bieckol-33 illustrated in Figure 10, have shown a potent inhibition of phospholipid peroxidation at 1μM in a liposome system and these phlorotannins have significant radical scavenging activities against superoxide and DPPH radicals effectively compare to ascorbic acid and α-tocopherol (16).

5.5. Anticancer activity

The available anticancer treatments such as ionizing radiation, hyperthermia, alkylating agents, DNA topoisomerase inhibitors and platinum compounds induce DNA damage indiscriminately killing both normal and rapidly proliferating cancer cell (108). Whereas, microalgal pigments protect normal cells from genetic damages and exert antiproliferative, cytotoxic and pro-apoptotic activities in cancer cells, suggesting their possible use for cancer prevention or chemotherapy (109). Two linear cytotoxic pentapeptides i.e. majuscule amide D-34 and deoxymajusuculamide D-35 are illustrated in Figure 11. Both have been isolated from a deep-water variety of the marine blue–green alga *Lyngby majuscule* (96). Usabamycins-37 are new anthramycin-type analogs isolated from Streptomyces sp. NPS853. Usabamycins show weak inhibition of HeLa cell growth and selective inhibition of serotonin (5-hydroxytrypamine) 5-HT2Buptake (98). Potential bioactive molecules such as microtubule polymerization inhibitors, curacin A-38, and dolostatin10-39, are in preclinical and clinical trials as anticancer drugs. Various derivatives of these molecules have been synthesized for drug development, for instance, TZT-1027 (solbidotin-40) is in phase I clinical trial and ILX-651 (tasidotin-45) is in phase II clinical trial, and LU-103793 is also understudied both structurally illustrated in Figure 12. These derivatives have improved pharmacokinetic and pharmacological properties than their natural counterparts (88,110). The antitumor activity of a synthetic derivative of dolostatin 10, TZT-1027 (solbidotin), was reported to be superior to existing anticancer drugs, including vincristin and paclitaxel for treating solid tumors. On the other hand, the synthetic analogue of the third generation dolostatin 15-42, ILX-651 (tasidotine), is also another potent antitumor drug candidate under development (20,88,110). A class of cyclic lipopeptide cyanobacterial metabolites, apratoxins, has excellent cancer cell cytotoxicity. This class of compounds represents a total of seven characterized apratoxins (A-44 to G-50) the most potent of them in cancer cell toxicity assay is apratoxin A-44 and F-49, showing a low sub-nanomolar LD-

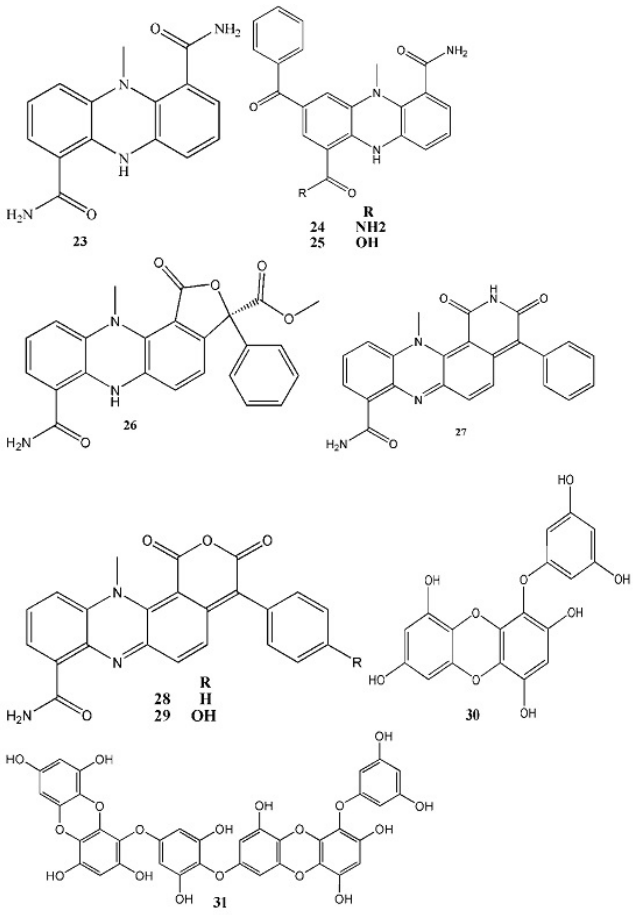

Figure 10. Potential antioxidant compounds isolated from microalgae.

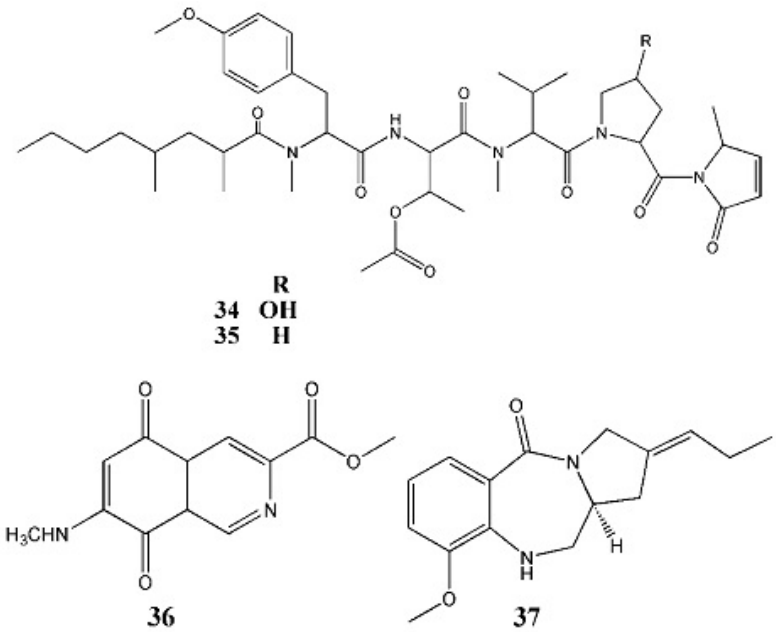

Figure 11. Bioactive compounds from microalgae with anticancer activity (majusculamide D (35), deoxymajusculamide D (36), Mansouramycin C (37) and Usabamycins (38).

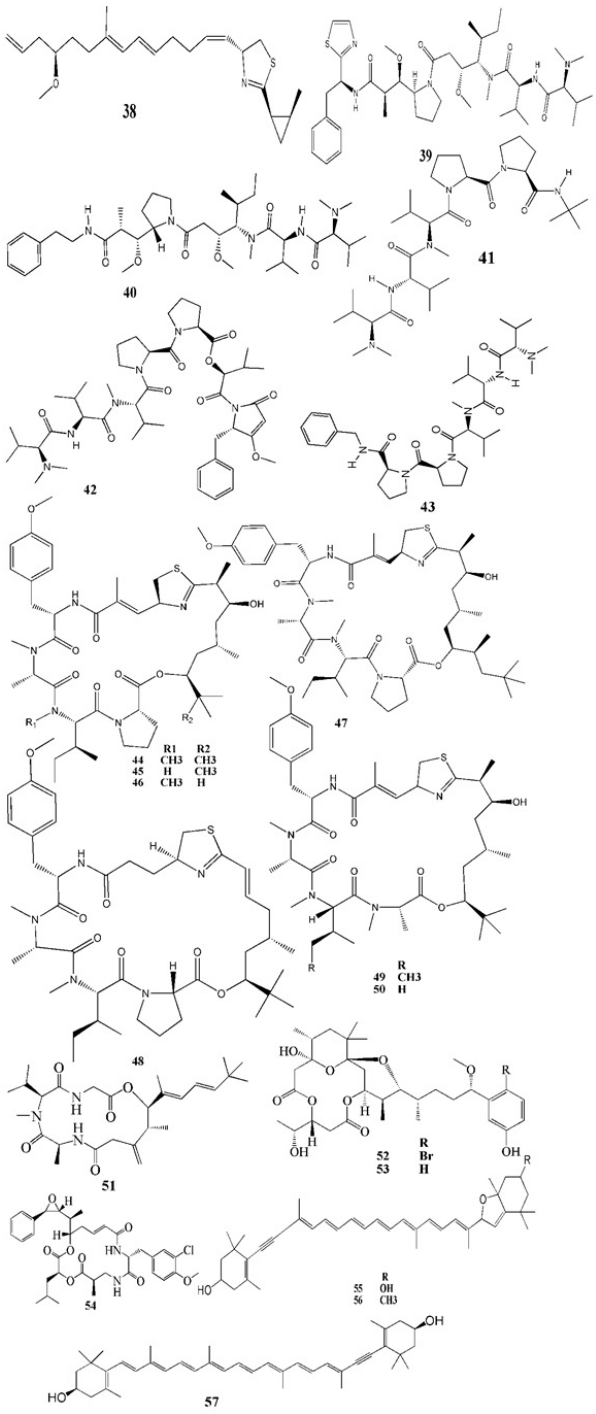

Figure 12. Microalgae derived anticancer agents in preclinical and clinical trial.

50 value in various cell lines (101). Antillatoxin-51, aplysiatoxin-52, and debromoaplysiatoxin-53 are also compounds isolated from microalgae responsible for such cytotoxic compounds as anticancer agents (111). Cryptophycin-54 from Nostoc species shows a fungicidal activity and rediscovered by Smith's group as a depolymerizing microtubule agent. The compound and its analogs are very efficient against solid tumors (96). Several acetylenic carotenoids belonging to diverse structural classes with cytotoxic activity against Raji cells (human neoplasm), three of which, viz. diadinochromes A-55 and B-56 and diatoxanthin-57/cynthiaxanthin, were isolated from *Peridinium bipes* (Dinophyceae). Diadinochrome

A-56 proved cytotoxic to HeLa cells, whereas the latter two exhibited unspecific anti-carcinogenic activity (50).

6. CONCLUSION

Microalgae are a potential producer of unique natural compounds with significant biological activities. Despite the fact that much research work has been published on high-value compounds of microalgae origin, the natural product research in the area is still in its infancy. There is a growing demand for high-value compounds of microalgae due to their importance in industrial applications as pharmaceutical, nutraceutical, cosmeceutical, animal feed, biological waste treatment, etc. Microalgae as prolific sources of bioactive molecules such as carotenoids, PUFAs, proteins, polysaccharides, glycolipids, which have been used or being trialed extensively to treat cancer, inflammation, Alzheimer, CVDs, malaria, leishmaniasis, TB, HIV, and others. In this regard, there has been a success in obtaining potent drugs and lead compounds like tasidotin and soblidotin, which are on clinical phase study as anticancer agents. Moreover, involving traditional biotechnology in the marine biotechnology could be a great leap towards finding high-value compounds with unique and multifunctional activities. Nevertheless, in contrast to the overwhelming species of marine microalgae yet to be researched only certain species are studied currently. The outcome of the researches on microalgae, being able to provide highly active compounds such as apratoxins, dolostatins, majusculamides, carotenes, is rather encouraging. Therefore, exploring newer and old microalgae species for novel compounds with better activity represents a productive research approach to advance the area of biotechnology at large and biomedical in particular to represent their notable potential for biotechnological and biomedical applications.

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