BIOMEDICAL POTENTIALS OF MARINE NATURAL PRODUCTS – AN OVERVIEW

1Bhuvaneshwari.J and 2Thirumalai Vasan.P

1Research Scholar, Department of Biotechnology, Srimad Andavan Arts and Science College (Autonomous), (Affiliated to Bharathidasan University, Tiruchirappalli) Thiruvanaikovil, Tiruchirappalli, Tamil Nadu, India

2Head of the Department, Department of Biotechnology, Srimad Andavan Arts and Science College (Autonomous), (Affiliated to Bharathidasan University, Tiruchirappalli) Thiruvanaikovil, Tiruchirappalli, Tamil Nadu, India

ABSTRACT:

Inflammatory diseases have become one of the major causes of health issues around the world, having a substantial influence on healthcare costs. With the recent developments in natural products, synthetic and combinatorial chemistry, there has been remarkable success in discovering and identifying natural products and their synthetic structural analogs that have anti-inflammatory activity. However, many of these therapeutics have signified deleterious side effects upon prolonged usage. Marine algae have been identified as an underexposed reservoir of unique anti-inflammatory compounds. These include polyphenols, sulfated polysaccharides, terpenes, fatty acids, proteins, and several other bioactive compounds. Consumption of these marine algae could provide defense against the pathophysiology of several chronic inflammatory diseases. With further analysis, it has been proved that algal anti-inflammatory phytochemicals have the inherent properties to be used as therapeutics or in the synthesis of structural analogs with profound anti-inflammatory activity with reduced side effects. This review will focus on the latest knowledge on the potential anti-inflammatory compounds discovered from marine algae.

Keywords: Marine Algae, Anti-inflammatory activity, Bioactive compounds, Skin disorders.

INTRODUCTION:

Inflammation is part of the non-specific protective response of the body towards any harmful stimuli such as bacteria, viruses, the fungus that damages the tissues, pathogens causing specific disease conditions, and also releasing harmful chemicals. (Ferraro-Miliani et al., 2007). It is the initiation of the body’s healing process that involves the white blood cells and chemical substances released from them. It is scientifically known that the body’s immune system initiates inflammatory processes, which are responsible for various signs and symptoms of the disease. While inflammation acts as a protective mechanism and helps in healing injury in most cases, it can also have deleterious side effects in many auto-immune diseases such as lupus and rheumatoid arthritis. In general, inflammation can be categorized into two different phases namely, acute and chronic. The acute phase is associated with the accumulation of fluids, elevated blood flow, increased vascular permeability, and the increase of the number of leucocytes and inflammatory mediators, whereas chronic inflammation is associated with the progression of specific humoral and cellular immune responses. (Feghali and Wright, 1997). Acute inflammation is short-term with effects subsiding in a few days, whereas in chronic inflammation the effects are long-lasting and lead to conditions like osteoarthritis and other auto-immune diseases. Chronic inflammation is the root cause of many lethal diseases for eg. Alzheimer’s disease, cancer, diabetes, stroke, kidney disease, skin diseases, and chronic lower respiratory disease. Commercially, blood tests detect proteins that are used as inflammatory markers with high sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α), fibrinogen, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8).

Since time immemorial, ancient civilizations have made use of plants, herbs, and their natural derivatives for the treatment and cure of various diseases. According to the World Health...
Organization, traditional especially herbal medicine has been used extensively around the world with over 80% of their member state's population practicing the natural way of treating diseases. Moreover, the entire scientific community has most often turned to medicinal plants as one of the major sources of biologically active substances to identify, characterize and understand the various mode of action of these numerous compounds found in these species. Many studies have shown to possess an anti-inflammatory potential that is found in plants and seaweeds and this helps to elucidate major inflammation pathways. However, despite all these, the pharmacological activities have so far been explicated for only a few of these species. (Sen and Samanta, 2014).

The Ocean which hosts the majority of the concentration of species on the planet has become the target of scientific interest around the middle of the 20th century. Since tapping into these natural resources, tens of thousands of new substances with pharmacological potential have been reported. Out of all the marine species living in the ocean, the one that sparks interest among researchers is the marine algae most commonly called seaweed. Marine algae are a promising source for new bioactive and pharmacological compounds. Seaweeds are generally photosynthetic autotrophic organisms that are classified into different taxonomic groups, which produce a range of chemically distinct compounds. Some of these compounds are not present in freshwater plants and hence they have distinct bioactive potential, of interest for pharmaceutics, cosmetics, and nutrition. Seaweeds are found to be potential sources of many biochemical compounds such as lipids, vitamins, proteins, polysaccharides, fibers, minerals, and others. (Catarino et al., 2018)

Consequently, in the same way, seaweed produces several secondary metabolites with remarkable biological activity, such as phenolic compounds, polysaccharides, carotenoids, lectins, steroids, polyketides, and many others. (Cardozo et al., 2007). A lot of research findings have shown that seaweeds contain a wide range of bioactive substances with various pharmacological potentialities such as antiviral, antibiotic and anti-endotoxic, antifungal antiparasitic, antioxidant, anti-aging, antinociceptive, anti-tumor, anti-diabetic, anti-inflammatory, and immunomodulatory effects. Out of all of these, the anti-inflammatory activity of those compounds that are derived from seaweeds contributes to one of the largest bioprospecting areas in marine natural products. (Cassio et al., 2020) This review will highlight inflammation associated diseases and the marine drugs that are used to treat them along with dietary interventions. The advancements made to discover novel anti-inflammatory drugs from marine algae could potentially bring new insight into the field of biomedical research.

**THE ROLE OF INFLAMMATION IN VARIOUS DISEASES:**

**DIABETES:**

Due to overnutrition, the body’s adaptive immune system, mainly that of the T lymphocyte and hyper levels of various cytokines and C-reactive protein can lead to glucose intolerance and may also induce the activation of the innate immune system in type 2 diabetic patients (Masters et al., 2011). There have been various studies that establish the fact that there are high levels of cytokines and acute-phase proteins in Type 1 and Type 2 diabetes mellitus. These cytokines such as IL-23, IFN-γ, and IL-17A contribute to the pathogenesis of type 1 diabetes (Fatima et al., 2016). Cytokines (IL-1 β, IL-6), plasminogen activator inhibitor, chemokines, and acute-phase proteins (CRP) are the main predictive indicators for the rapid progression of Type 2 diabetes mellitus (Herder et al., 2009). This process of inflammation generates the synthesis of advanced glycation end-products (AGEs) like glycated proteins and lipids, and/or insulin resistance that leads to diabetes (Hajjar et al., 2017). These advanced glycated products in turn interact with their receptors on macrophages and thereby generates reactive oxygen species (ROS). This further induces inflammation and also activates nuclear factor-kB (NF-kB), resulting in the facilitation of transcription of the inflammatory cytokine genes (Deeb et al., 2016).
Preclinical studies of antihyperglycemic drugs have revealed anti-inflammatory effects at a much higher concentration than those that have been used in clinical practice. Their anti-inflammatory activity is mediated by direct modulation of the immune system or by their metabolic effects on hyperglycemia and hyperlipidemia. Antidiabetic drugs like biguanides, sulphonylureas, thiazolidinediones, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase 4 inhibitors, and insulin decrease CRP and other inflammatory markers and may play a beneficial role in inflammatory conditions. Among all these classes, thiazolidinediones have shown the most consistent anti-inflammatory effect in comparison to moderate activity by others (Pollack et al., 2016).

HEART DISEASES:
Several clinical studies have shown strong and consistent relationships between markers of inflammation and associated risk of cardiovascular disease. A long-known marker, C-reactive protein (CRP), increases and indicates the presence of any type of inflammation in the body (Shrivastava et al., 2015). Hence, an elevated level of CRP has been known to be directly linked to heart disease and is now considered as an important indicator of heart disease than high low-density lipoprotein (LDL) cholesterol (Ridker, 2002). The cardiovascular effects such as the generation of oxygen radicals, clotting, increase in the expression of adhesion molecules, and plasminogen activator inhibitor-1 and plaque destabilization are mediated by CRP and lead to heart disease (Prasad 2006).

BONE HEALTH:
The osteoclast and osteoblast cells are responsible for the overall bone health in the body. When osteoporosis occurs, there is an imbalance in osteoclasts which results in dissolving more bone than what osteoblasts can generate. Bone resorption is usually modulated by inflammation with the help of two mechanisms: The first is the pro-inflammatory cytokines that mediate osteoclast function through receptor activator of nuclear factor-B and also its functional ligand and the second is by the mechanism of modulation by the macrophage colony-stimulating factor. Several cytokines that are related to osteoclast bone resorption are TNF-α, interleukin (IL)-1, IL-6, IL-11, IL-15, and IL-17 (Tanaka et al., 2005). Clinical studies have indicated that there are significant levels of reduction in the serum levels of CRP in humans due to calcium fructoborate. It is a sugar-borate ester and a plant–mineral complex which helps fight the inflammation that is associated with the loss of bone mineral density (Scorei, 2013).

AGGRESSION, ANXIETY, AND ANGER DISORDERS:
Recent studies have shown a direct relationship between plasma inflammatory parameters and aggression in humans. The markers of inflammation, which are the plasma CRP, and IL-6 were known to be elevated in patients with the intermittent explosive disorder (IED) compared with that of the psychiatric or normal controls. It is not yet clear if the inflammation provokes aggression or whether aggression triggers inflammation. Both have been known to be biologically connected and thereby form a damaging combination (Coccaro et al., 2013). Healthy people with anger, anxiety, and depression have high CRP levels in the blood. Both animal and human studies have so far confirmed the relation between peripheral cytokines and the occurrence of aggression and display hostility-like symptoms (David Klonsky et al., 2011). IL-6 and IL-1 β have already been correlated with anger and hostility respectively. It has been suggested that targeting the inflammatory system for potential biomarkers to treat and identify patients possess an increased risk with symptoms such as anger, aggression, and suicidal tendencies (Brundin et al., 2015).
ANTI-INFLAMMATORY ACTIVITY OF MARINE NATURAL PRODUCTS:

For the treatment of chronic inflammation-associated lethal diseases, new drug discovery is of the greatest value, and this can lead to the development of new drug candidates for safe and effective therapy. Many natural sources have been exploited for the isolation of anti-inflammatory natural products during the last few decades. This review focuses on recent products that are available from various marine sources for their current status.

MARINE PLANTS:

When it comes to scientific research, marine plants have rarely been discussed in the literature as a distinct and self-contained group. Generally, marine plants have always been understudied and commonly treated as poor relations with those of marine animals in courses and texts related to marine biology. Marine algae which are treated as marine plants tend to lose their essentiality and disappear among the taxonomical and morphological parallels with that of their freshwater algal counterparts. Over 90% of marine plant species are algae. Since, there happens to be considerable chemical diversity in marine plants, including marine algae and mangroves, the marine natural products isolated from these plants have been shown to possess antibacterial, antifungal, analgesic, anti-inflammatory, anti-cancer, cytotoxic, hypotensive, and spasmogenic activities. (Orlikova et al., 2014).

MARINE ALGAE:

Among marine sources, algae have been the most exploited and they have yielded a large number of unique anti-inflammatory compounds. Marine algae, commonly known as macroalgae or seaweed, are photosynthetic eukaryotic organisms that are mostly found in coastal areas with persistent vitality. To be able to survive in such utmost environmental and diversified conditions, macroalgae produces a variety of natural bioactive compounds and metabolites, such as polysaccharides, polyunsaturated fatty acids, and phlorotannins (Hultberg et al., 2013). Since macroalgae are one of the most widely studied and used marine resources, bioactivities of these constituent components of marine algae have been widely investigated. The bioactive compounds such as polyphenols exhibit anticancer, antidiabetic, antioxidant, and anti-inflammatory activities (Fernando et al., 2016). Table 1 composes potential anti-inflammatory extracts/compounds derived from marine algae. Most of these compounds have shown to exhibit anti-inflammatory activity by reducing the levels of IL-6, TNF-α, NO, and PGs, and inhibiting COX, iNOS, NFκB, and STAT activity (Lee et al., 2013).

MARINE SPONGES:

Marine sponges are one of the richest natural sources known for their unique bioactive compounds due to their environmental and ecological conditions. They have been proven to be an excellent source of compounds exhibiting enzyme inhibition, anti-tumor, anti-inflammatory, antiviral, anti-bacterial, immunosuppressive, analgesic, anti-diabetic, and cardiovascular properties. There is a continuous search for anti-inflammatory compounds from sponges and they have been so far reviewed by several authors (Kumar et al., 2016). Table 2 lists the anti-inflammatory compounds isolated from marine sponges over the years. The majority of these compounds from sponges are dominated by terpenoid and sesterterpenes class compounds (Keyzers and Davies-Colemane, 2005).

BRYOZOANS:

Bryozoans are aquatic and benthic invertebrates that grow by encrusting rocky surfaces, shells, or algae. Their colony sizes range from a few millimeters to meters. Bryozoans are reported to produce a variety of chemical compounds that exhibits antifouling and antipredatory properties. Very little research has been undertaken on the bryozoans for their anti-inflammatory bioactive compounds due to the lack of biomass and taxonomy details as compared to other marine invertebrates (Blunt et al., 2013). There are very few reports on the anti-inflammatory activity of bryozoan. Studies have
reported the anti-inflammatory activity in NFκB, TNF-α, and IL-1β screening of *Eucratea loricata*. In another study, the diethyl ether extract of *Zoobotryon verticillatum* also showed anti-inflammatory activity at 100mg kg⁻¹ in the carrageenan rat model. (Sankar et al., 2013).

### ROLE OF MARINE ALGAE IN TREATMENT OF SKIN DISORDERS:

#### ALGAE FOR MELANOMA TREATMENTS:

One of the most common malignancy tumors is skin cancer. Skin cancers can be differentiated into three different types. These are basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinoma and squamous cell carcinoma can be classified as non-melanoma skin cancer. Melanoma, which is derived from melanocytes, is the most aggressive and most common type of skin cancer. Most melanomas range from various colors such as from brown to black, and sometimes are seen with a pink, red, or fleshy appearance which are more aggressive, and these come along with symptoms such as itching or bleeding. Both genetic and environmental factors could be responsible for skin cancer, such as fair skin, exposure to sunlight, and multiple benign naevi (Garbe and Leiter, 2009).

Overexposure to UV radiation is the most important risk factor for skin cancer. Many experimental animal studies have shown that repeated exposure to UV radiation can lead to skin cancer (Cordeiro-Stone et al., 2016). Thus, usage of sunscreen and avoiding exposure to UV radiation are some of the most effective methods to prevent skin cancer. Other treatments such as surgery, chemotherapy, radiation therapy, and targeted therapy are also necessary. Usually, available chemotherapy drugs contain higher cytotoxicity and side effects, which could be harmful to other body organs, even reducing the quality of life and exacerbate disease condition. One such instance shows the treatment of CTLA-4 antibody therapy in metastatic melanoma resulted in autoimmune-mediated side effects like otitis, hypophysitis, hepatitis, and iridocyclitis may occur. Exploring more safe and effective drugs for skin cancer is in urgent need. Antitumor and cytotoxic compounds have been found from marine algae, such as polysaccharides from *Sargassum fusiforme* with anti-liver cancer activity (Fan et al., 2017).

#### MARINE ALGAE AGAINST ACNE VULGARIS:

Acne vulgaris, commonly known as acne, is a skin disease or condition that affects many adolescents and young adults. It is usually characterized by blackheads or whiteheads, pimples, greasy skin, and possible scarring. Acne can persist for years and result in permanent scars, disfigurement, and has adverse effects on the physiological development of a person. The pathogenesis of acne is complex and is based on multiple factors. Generally, it is viewed as an inflammatory disease. Some of the other factors such as hair follicle keratinization, sebum secretion, and bacteria can also contribute to acne (Farrar et al., 2004).

Acne vulgaris caused by bacterial growth has been traditionally treated with antibiotic therapies such as clindamycin and erythromycin. However, the extensive application of these antibiotics has led to bacterial resistance. Besides, antibiotics may cause skin allergies such as rashes and skin irritation. Consequently, the bioactive compounds extracted from marine algae could be a safe and natural alternative. Marine macroalgal extracts have been reported to possess antibacterial and antifungal activities (Pérez et al., 2016). Different extracts of various marine algae were examined for their antibacterial activity against skin bacteria. Also, extracts from some macroalgae were shown to exhibit anti-inflammatory effects and can modulate the levels of growth factors and collagen, which could improve the acne skin condition and speed up skin repair. (Lee et al., 2009).

#### MARINE ALGAE FOR THE TREATMENT OF ATOPIC DERMATITIS:

Atopic dermatitis (AD) is a pruritic inflammatory skin disorder that can be associated with a personal or family history of allergic patients. AD can occur at any age and it most often affects...
infants and young children. (Niggemann et al., 2008). In some instances, it may also persist into adulthood or might appear even later in life. The prevalence of AD is on the rise and has been estimated at ~17% in the USA. The fundamental lesions in AD are due to a defective skin barrier that results in dry itchy skin, and this is also aggravated by the mechanical injury inflicted by scratching. This condition allows the entry of antigens via the skin and creates a milieu that further triggers the immune response to these antigens (Noval et al., 2003). Clinical observations have so far suggested that AD is the cutaneous manifestation of a systemic disorder that could give rise to asthma, food allergies, and allergic rhinitis.

These days, marine algae-derived phlorotannins have been investigated for their human beneficial aspects that include anti-oxidant, anti-inflammatory, and hyaluronidase inhibitory activities. Most notably, one of the new phlorotannins called phlorofucofuroeckol-B, which was isolated from Eisenia arborea, an edible brown algae has been occasionally used as a folk medicine in gynecopathy in Japan. In vitro studies conducted on rat basophile leukemia (RBL)-2H3 cells have confirmed that this new phlorotannin is capable of inhibiting histamine release thereby confirming its anti-allergic potentiality. The bioactive compounds isolated from Eisenia arborea such as eckol, 6,6′-bieckol, 6,8′-bieckol, 8,8′-bieckol, phlorofucofuroeckol-A, and phlorofucofuroeckol-B have been reported to exhibit anti-allergic properties that are similar to, or even greater than the typical inhibitor for allergies, epigallocatechin gallate. Among these, Phlorofucofuroeckol-B has been shown to have the most potent activity of all the tested phlorotannins. This also suggests that this compound has a greater anti-allergic activity at approximately 2.8 times greater than that of epigallocatechin gallate. All of this research has proved that there should be a need for more advanced scientific investigations and animal model studies to unravel the molecular mechanism of phlorotannins as potent anti-inflammatory substances. (Sugiura et al., 2007). Hence it has been shown that these studies could most possibly confirm the efficacy of marine polyphenolic compounds as potential cosmeceutical leads for the formulations of lotions and creams to cure AD.

MARINE ALGAE USED FOR THE REDUCTION OF SKIN PIGMENTATION:

Melanin is quite a broad term that is used for a group of natural pigments found in most organisms. In the skin, melanogenesis occurs after oxidative stress, especially once there is exposure to ultraviolet (UV) radiation (Lee et al., 2013). Melanin is an effective absorber of light, hence it is thought to protect the skin cells from damage caused by UV radiation. Generally, melanin is produced by melanocytes located in the basal epidermal layer. However, if the skin gets enhanced oxidative stress, it causes hyperpigmentation, and it is of utmost concern. The melanin synthesis involves the tyrosinase which acts as the rate-limiting oxidase to catalyze eumelanin and phenomelanin synthesis (Solano et al., 2006). The formation mechanisms of both these pigments (eumelanin and phenomelanin) are the same. The process includes the conversion of tyrosinase catalyzed L-tyrosine hydroxylation to 3, 4-dihydroxy-L-phenylalanine (L-DOPA) and then L-DOPA oxidation to dopaquinone. Therefore, tyrosinase inhibitors are thought to be an important and efficient constituent for depigmenting, and hence these act as whitening agents (Liang et al., 2012). However, chemical tyrosinase inhibitors may cause some drastic side effects.

Thus, when searching for safe and effective skin whitening agents, marine algae has been proved to be beneficial for the cosmetic industry. To find new anti-browning and whitening agents, scientists screened various marine algae for tyrosinase inhibitors, and as a result, have found some potential algae. An investigation has been done on 43 indigenous marine algae for their tyrosinase inhibitory activity and it has been found that the extracts from Endarachne binghamiae, Schizymenia dubyi, Ecklonia cava and Sargassum silquastrum exhibited potent tyrosinase inhibitory activity similar to kojic acid (Cha et al., 2011).
MARINE NATURAL PRODUCTS AS A SOURCE OF POTENTIAL BIOACTIVE SECONDARY METABOLITES:

One of the major concerns in medicinal research is the anti-inflammatory properties of marine algae bioactive. These marine algae metabolites help in providing desirable protective effects against the pathogenesis of chronic inflammatory diseases and could help replace the synthetic drugs that are currently in use. Based on these novel advances in natural product research, there have been numerous anti-inflammatory compounds that are being isolated from marine algae. This review also highlights the various classes of anti-inflammatory compounds isolated from marine algae up-to-date and their potential application as candidates for anti-inflammatory drug development and as key ingredients in nutraceutical products to prevent inflammatory disorders.

MARINE PHENOLIC COMPOUNDS THAT POSSESS ANTI-INFLAMMATORY ACTIVITY:

Phenolic compounds represent a large and diverse group of secondary metabolites that comprises one or more phenyl groups. These well-known phytochemicals are biosynthesized through shikimate acid and acetate-malonate pathways (Tsao, 2010). Based on their fundamental structural properties phenolic compounds ranges from simple phenols to complex molecules such as phenolic acids, flavonoids, phlorotannins, coumarins, lignins, lignans, stilbenes, and their derivatives (Khoddami et al., 2013). Phenolic compounds are mostly known for their comprehensive biological functionalities such as anti-oxidant, anti-inflammatory, anti-cancer, anti-microbial, and many more. (Cai et al., 2004).

Marine algae especially marine brown alga have been widely studied for their rich source of phenolic compounds. Particularly, the phlorotannins from brown algae have been known to act as inhibitors of proinflammatory cytokines such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1) and interleukin-6 (IL-6) in lipopolysaccharides (LPS) stimulated microglial cells (BoMi and Se-Kwon, 2012).

MARINE POLYSACCHARIDES AS POTENT ANTI-INFLAMMATORY DRUGS:

Polysaccharides are classified as an important category of compounds that are not exactly drugs but are used in the pharmaceutical industry as drug carriers, e.g. chitin, chitosan, alginate, agar, and carrageenans. Some of the major sources of chitin are the shell wastes of shrimps, lobsters, and crabs. Marine polysaccharides display their anti-inflammatory properties by interfering with the migration of leukocytes mainly at the site of inflammation and thereby binding with the surfaces of polymorphonuclear cells. They are capable of acquiring various shapes and sizes. Their responses in biological studies have been dependent on various external stimuli, such as pH and temperature.

These properties make them excellent biomaterials for the construction of carrier devices in the commercial manufacture of drugs, nano- or microparticles, capsules, and hydrogels. Orally administered chitosan oligosaccharides exhibited suppression in inflammatory processes and showed expression of NF-κB, COX-2, iNOS, and pro-inflammatory cytokines (Azuma et al., 2015). Chitosan, fucoidans, and microcapsules from cnidarians are some of the few examples which have been so far taken up and explored for drug-delivery systems from marine source. These results offer considerable potential to be used in place of synthetic biomaterials.

ROLE OF FUCOIDAN IN SKIN DISEASES TREATMENT:

Marine macroalgae have been considered as one of the major dietary components and also as alternative medicine in many Asian countries like Japan, Korea, and China. Marine algae produce different polysaccharides that include carrageenans, alginates, laminarans, and fucoidans.
These contain large quantities of L-fucose and sulfate, together with slight amounts of other sugars such as xylose, galactose, mannose, and glucuronic acid. (Bilan et al., 2010) Fucoidans obtained from marine algae have been reported to exhibit exceptional biomedical activities that aid in human health. Fucoidans are those sulfated polysaccharides that are exclusively found in seaweeds in their cell walls. This polysaccharide ingredient is largely composed of a polymer $\alpha1\rightarrow3$-linked 1-fucose with sulfate groups on some of the fucose residues at 4 positions.

Fucoidans are being studied extensively due to their potential antitumor, antiviral, anti-complement, and other anti-inflammatory activities. When it comes to skin-related diseases, UV-B reduces type I procollagen levels and increases MMP-1 levels in human skin, and also plays a major role in the process of photoaging. This process of UVB-induced MMP-I expression at the protein and mRNA levels in human skin fibroblasts (HS68) are obstructed by fucoidan. Various research has proved that fucoidan treatment has also increased type I procollagen mRNA and protein expression in a dose-dependent manner compared to the control. This as a result indicates that fucoidan may prevent UVB-induced MMP-I expression and inhibit down-regulation of type I procollagen synthesis. Research on these polysaccharides derived from marine algae has shown that fucoidan may act as a potential therapeutic agent to prevent and treat skin photoaging (Moon et al., 2009).

**MARINE ALGAL ALKALOIDS THAT POSSESS ANTI-INFLAMMATORY ACTIVITY:**

Marine algal alkaloids comprise a vast group of natural marine products that contain nitrogen groups. Hordenine was the first marine alkaloid that was isolated from marine algae in 1969 that exhibited potential diuretic activity. Although alkaloids from terrestrial plants have been widely explored, only a few studies have been reported regarding the alkaloids obtained from marine algae. Caulerpin that contains two indole groups was revealed to be the only alkaloid isolated from green algae that belong to Caulerpa genus.

Red algae of the genus Gracilaria have also been described as vital sources of anti-inflammatory compounds and alkaloids with elucidated biological activity. As studies have shown, it has been observed that the aqueous extract of *Gracilaria tenuistipitata* exhibited anti-inflammatory activity in an *in vitro* Hepatitis C Virus (HCV) - induced inflammation model. (Chen et al., 2013). Further investigations are in need to explore the anti-inflammatory potentials of marine algal alkaloids. (Fernando et al., 2016).

**TERPENOIDS, STEROLS AND CAROTENOIDS FROM MARINE ALGAE WITH ANTI-INFLAMMATORY PROPERTIES:**

Terpenoids consist of a large group of secondary metabolites that are assembled by isoprene units that contributes to a vast structural and functional diversity. Based on this number of isoprene units, terpenoids can be classified into mono-, sesqui-, di-, sester-, tri-, and tetraterpenoids. Sterols are derivatives of triterpenoids that consist of 6 isoprene units. Fucosterol is the predominant sterol in brown algae with several different bioactivities. Cholesterol is abundant in red algae, whereas green algae consist of a variety of steroids. Carotenoids can also be categorized under terpenoids as they are tetraterpenoid derivatives with 8 isoprene units (Balboa et al., 2013).

The different process of biosynthesis of terpenoids such as sterols proceeds through the acetate/mevalonate pathway, whereas terpenoids that include carotenoids and phytol proceed through the 1-deoxy-d-xylulose-5-phosphate pathway. Among all these known anti-inflammatory drug categories, steroidal compounds, glucocorticoids are the most potent anti-inflammatory substances compared to other non-steroidal anti-inflammatory drugs. (Fernando et al., 2016).

**BIOPROSPECTING OF MARINE NATURAL PRODUCTS:**
The marine biome is currently one of the largest sources of biologically active compounds, offering a great possibility of bioprospecting for new pharmacological treatments. Microalgae and macroalgae are organisms with great potential for bioprospecting marine natural products and are rich sources of compounds with already characterized antimicrobial, antitumor, anticoagulant, and anti-inflammatory activity (Liu et al., 2018).

Ocean holds vast opportunities for the exploitation of a wide variety of bioactive compounds with potential anti-inflammatory effects. Although it is to be noted that cancer and cardiovascular diseases may stay as the main indications, a further extension of spectrum indications could be expected shortly. To explain this further, a variety of marine compounds share anti-inflammatory function. With the futuristic scope for their broad application prospects, it can be expected that certain anti-inflammatory agents that are presently used in clinical applications are supposedly expected to be either partly replaced or concurrently used with marine-derived natural products for higher safety and less toxicity. (Shinde et al., 2019). Particularly to specify, marine algae could also yield a wide array of anti-inflammatory compounds such as terpenes, polyphenols, sulfated polysaccharides fatty acids, proteins, and several other molecules thereby signifying the potential for natural marine products that could act as templates for the discovery of anti-inflammatory agents and compelling synergistic effect (Fernando et al., 2016).

CONCLUSION AND FUTURE PROSPECTS:

Marine organisms have been well studied for their anti-inflammatory potential. However, algae and sponges are notably the most investigated sources whereas others like bryozoans, echinoderms, molluses, phytoplankton, and tunicates are so far less explored. Marine algae are known to be rich sources of bioactive compounds with antibacterial, anti-tumor, and anti-oxidative properties. As a result, there is increasing attention has been paid to the application of marine algae in pharmaceutical, cosmetic, and food industries. Studies have been mostly carried out for extracts. However, isolation and identification of bioactive constituents are still limited. One of the major challenges that are being faced right now with these studies is the erosion of marine biodiversity. Hence, alternative tools like functional metagenomics and genome sequencing can be used to widen the scope of drug discovery from the habitats of extreme environmental conditions of the ocean. The majority of the marine polysaccharides exhibit anti-inflammatory activity and so, these could be made use of as potent drug carriers for controlled drug release. There is further scope of using algal extracts as effective bioactive ingredients in the treatment of skin disorders and also for skincare. There is also a much need for the emphasis on safe and targeted delivery of drugs for the treatment of various disorders.

<table>
<thead>
<tr>
<th>MARINE ALGAE NAMES</th>
<th>EXTRACT/COMPOUND</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Alexandrium minutum</em></td>
<td>Acetone extract</td>
<td>Lauritano <em>et al.</em>, 2016</td>
</tr>
<tr>
<td><em>Caulerpa mexicana</em></td>
<td>Methanol extract</td>
<td>Bitencourt <em>et al.</em>, 2015</td>
</tr>
<tr>
<td><em>Gelidium sesquipedale</em></td>
<td>Methanol, Hexane, Dichloromethane, and Water extract</td>
<td>Boujaber <em>et al.</em>, 2017</td>
</tr>
<tr>
<td><em>Lithothamnion corallioides</em></td>
<td>Aquamin</td>
<td>Ryan <em>et al.</em>, 2010</td>
</tr>
<tr>
<td><em>Nannochloropsis oculata</em></td>
<td>Sterol rich fraction</td>
<td>Sanjeeva <em>et al.</em>, 2017</td>
</tr>
<tr>
<td><em>Pavlova lutheri</em></td>
<td>Lipid extract</td>
<td>Robertson <em>et al.</em>, 2015</td>
</tr>
<tr>
<td><em>Solieria filiformis</em></td>
<td>Lectin</td>
<td>Abreu <em>et al.</em>, 2016</td>
</tr>
</tbody>
</table>
**Sargassum wightii**

Benzoic acid, Diethyl phthalate, Methyl salicylate, 2-Hydroxy-ethylester, Hexadecanoic acid, Ethyl ester, and (E)-9-octadecenoic acid ethyl ester

Balachandran et al., 2016

**Undaria pinnatifida**

Methanol extract

Hwang et al., 2014

Table 1: Marine algae derived potential anti-inflammatory agents

<table>
<thead>
<tr>
<th>SPONGE’S NAME</th>
<th>COMPOUNDS</th>
<th>REFERENCES</th>
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<tbody>
<tr>
<td>Aplysina aerophoba</td>
<td>Aeroplysinin-1</td>
<td>Garcia- Vilas et al., 2015</td>
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<td>Scalarispongia aqabaensis</td>
<td>Scalaristerol</td>
<td>Mencarelli et al., 2013</td>
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<tr>
<td>Theonella swinhoei</td>
<td>Solomomoster A</td>
<td>Mencarelli et al., 2013</td>
</tr>
<tr>
<td>Haliclona sp.</td>
<td>Halipeptins A and B</td>
<td>Randazzo et al., 2001</td>
</tr>
<tr>
<td>Dysidea avara</td>
<td>Avarol, Avarone</td>
<td>Ferranditz et al., 1994</td>
</tr>
<tr>
<td>Dactylospongia elegans</td>
<td>Dactylothioline B</td>
<td>Lee et al., 2015</td>
</tr>
</tbody>
</table>

Table 2: Marine Sponge Natural products with anti-inflammatory properties

REFERENCE:
impact. Comparative Biochemistry and Physiology Part C Toxicology and Pharmacology, 146, 60–78.