Novel marine terpenoids show great promise as a source for new antioxidant agents in cosmetic preparations [8,9], due to their good penetration-enhancing abilities, low systemic toxicity and low irritation. Fucosterol (Figure 1) is a steroidal terpenoid extracted from Phaeophyta marine algae (*Ecklonia stolonifera, Pelvetia siliquosa, Sargassum carpophyllum*) [10-12]. Fucosterol is usually obtained as a primary compound from the non-polar fraction of algae extract [10]. This compound shows strong antioxidant activity by increasing the concentration of antioxidant enzymes Superoxide Dismutase (SOD), catalase and glutathione peroxidase (GSH-px), enzymes that are involved in the fine control of cellular H_2O_2 concentration. Fucosterol can help in cellular defense mechanisms by preventing cell membrane oxidation as it has an important role in scavenging hydrogen peroxide and restoring SOD activity. Similarly, an increase in GSH-px activity indicates that fucosterol also helps in the restoration of vital endogenous antioxidants such as gluthathione [11,13].

There are two types of antioxidants in human cells, enzymatic and non-enzymatic, that play significant roles in protecting cells from oxidative stress. The enzymatic antioxidants are SOD, catalase and GSH-px, and glutathione reductase. The first three enzymes directly catalyze the transformation of peroxides and superoxides to nontoxic species. Glutathione reductase reduces oxidized glutathione to glutathione, a substrate for glutathione peroxidase.

The most important non-enzymatic antioxidants are vitamins C and E, β-carotene and coenzyme Q10 (ubiquinone, ubidecarenone) [13]. Extrinsic environmental effects such as UV irradiation initiate and activate a complex cascade of biochemical reactions in human skin causing depletion of these enzymes. The skin of aged and photo-aged individuals has reduced levels of natural enzymatic and non-enzymatic antioxidants and reduced capacity to fight oxidative stress and the associated Reactive Oxygen Species (ROS), free radicals that lead to aging. ROS are formed when oxygen combines with other molecules resulting in oxygen species with an unpaired electron.

The inflammatory process in the skin is a result of accumulation of ROS. ROS have a major role in photo-aging of human skin *in vivo* [13-15], by causing oxidative damage to cellular DNA, proteins, membrane lipids and carbohydrates, which accumulate in the dermal and epidermal compartments. Photo oxidative damage is the result of UV irradiation due to the generation of ROS [16]. Erythema development, premature aging of the skin, progression of photo dermatoses, and skin cancer are the result of photo oxidative damage [17]. Degradation of fibrillar collagen that occurs in photo damaged skin is a result of up regulation of MMPs.

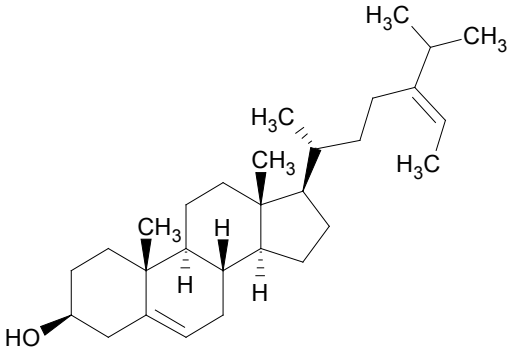

Figure 1: Fucosterol.

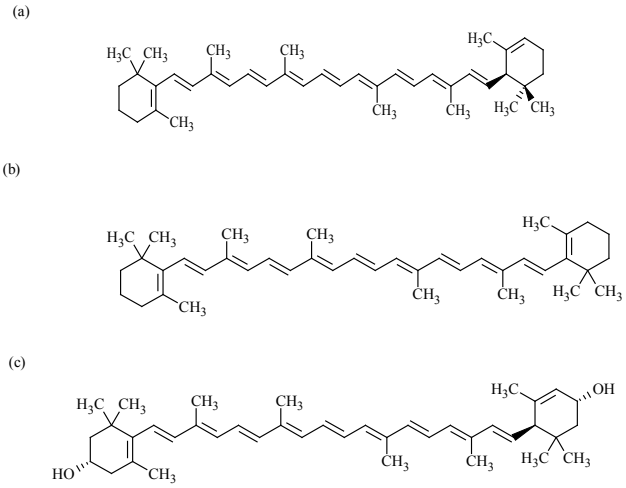

Figure 2: Naturally occurring carotenoids (a) α-carotene; (b) β-carotene and (c) xanthophyll.

ROS also lead to the formation of Matrix Metalloproteases (MMPs) in the skin[18]. MMPs are major enzymes involved in the remodeling of the extracellular matrix by proteolytic degradation of collagen and elastic fibres, resulting in the loss of the skin's ability to resist stretching. In normal skin, MMPs are expressed in very low levels and are kept inactive [13].

Carotenoids: Carotenoids are a diverse class of naturally occurring tetraterpenoid molecules that are synthesized by plants, bacteria, fungi and algae. They have been found to have a defensive role in the protection of cells and tissues from oxidative stress [19]. Some carotenoids function as direct quenchers of reactive oxygen species [20]. All photosynthetic eukaryotes are able to synthesize lycopene, a C40 polyene, which is the precursor for two different carotenoids, the β,ε-carotene (α-carotene) and the β,β-carotene (β-carotene) [21]. Xanthophylls are oxidation products of the carotenes, and diversification of xanthophylls increases by the inclusion of allene or acetylene groups.

Allenic and acetylenic carotenoids, such as fucoxanthin and neoxanthin, respectively [22], are highly represented in red algae, and at least 30 different carotenoids have been identified in this group [23]. The distribution of carotenoids having different molecular structures or the presence of specific biosynthesis pathways involving particular carotenoids can be used as chemotaxonomic markers for algae classification [24].

In plants, carotenoids have at least a triple function. They serve as pigments [25], stabilize chlorophyll-protein complexes [26-28], and protect the organism from excessive UV radiation [29]. The most important mechanisms of light protection are xanthophyll cycles. Most red algae exhibit a simple xanthophyll pattern, α carotene (Figure 2a) and/or β-carotene (Figure 2b) and one major xanthophyll (Figure 2c), either lutein or zeaxanthin.

The extent of absorption, transportation and excretion of a carotenoid is mostly based on its lipophilicity [19]. As they are lipophilic molecules, carotenoids are likely to accumulate in lipophilic compartments like membranes or lipoproteins. Carotenoids present in lipophilic compartments readily react with peroxyl radicals [30] and hence protect cellular membranes and lipoproteins from oxidative destruction due to their lipophilicity and ability to scavenge peroxyl radicals [19].

Tocopherol

Tocopherols are lipid soluble compounds with α-tocopherol (Figure 3) being the main source of vitamin E in the body, and with the RRR-α-tocopherol stereoisomer (natural or d-α-tocopherol) having the highest antioxidant activity. Vitamin E refers to a family of at least eight fat soluble compounds that include both four main tocopherols and four main tocotrienols. They consist of a polar chromanol ring, which is the site of antioxidant activities, and a hydrophobic aliphatic side chain (C-12) containing two methyl groups in the middle and two more at the terminal position. For the four tocopherols the side chain is saturated, whereas for the four tocotrienols the side chain contains three double bonds, all of which adjoin a methyl group.

The four tocopherols and the four tocotrienols have an alpha, beta, gamma and delta form based on the number (three, two and one) and position of the methyl groups on the chromanol ring [31]. The alpha form of tocopherol constitutes about 90% of the tocopherol in animal tissue, originally designated d-alpha-tocopherol on the basis of optical activity. There are actually three asymmetric carbon atoms in tocopherol, one at the 2-position of the chromanol ring, and the other two on the aliphatic chain, at the 4' and 8' positions - all being locations of methyl groups. Photosynthetic organisms produce α-tocopherol as a protective barrier against UV irradiation. Due to its anti-oxidant properties, the use of α-tocopherol is thought to be useful in preventing light-induced pathologies of human eyes and skin [32]. The algae species *Dunaliella tertiolecta* and *Tetraselmis suecica*, widely used in the aquaculture industry as a feed for fish, also produce relatively high concentrations of α-tocopherol [7].

Vitamin E protects the viability of cell membranes which are composed mainly of polyunsaturated fatty acids and are susceptible to lipid peroxidation from free radicals. Due to their lipophilicity and ability to scavenge peroxyl radicals, tocopherols play an important role in the protection of cellular membranes and lipoproteins against oxidative damage. As tocopherol is absorbed it acts as an antioxidant, preventing oxidation by donating hydrogen atoms to lipid and lipid peroxyl radicals. Vitamin E also acts directly as an antioxidant by quenching singlet oxygens and superoxide anions. The ability of beta-carotene and other carotenoids to quench excited oxygen is limited, because the carotenoid itself can be oxidized during the process (autoxidation).

The anti-oxidising properties of vitamin E are enhanced by the presence of glutathione and ascorbic acid, as they donate hydrogen atoms to the tocopherol radical converting it back to its unoxidised form. Vitamin E has also been thought to help prevent the breakdown of collagen in the skin. Fibroblasts (of older individuals) were incubated with α-tocopherol, resulting in levels of interstitial collagenase (MMP-1) being significantly reduced with no change in tissue inhibitor of MMP expression detected. MMP-1 is involved with the breakdown of collagen and destruction of the extracellular matrix, therefore the use of α-tocopherol in topical products may help protect the dermis from breaking down provided it is present at high enough concentrations [33].

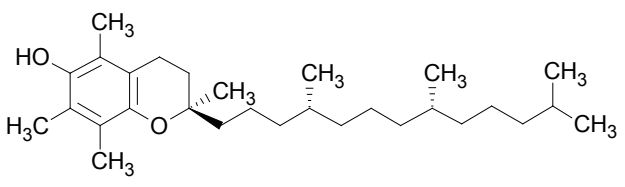

Figure 3: α-Tocopherol.

Topical antioxidants are generally used in combination with sunblocking agents, as they are inefficient UV filters with low SPF (Sun Protection Factor). Various studies have shown that vitamin E can act as a protective agent to reduce the physical appearance of aging due to sun exposure when used as an excipient in combination with sunblocking agents. When α-tocopherol is exposed to radiation, it converts to UV-absorbing dimer and trimer, which act in a similiar fashion to sunscreen agents. However, α-tocopherol acetate has not shown efficacy even though it is widely used in commercial sunscreen products. α-tocopherol acetate has a lower photoprotective effect due to its absorption over a lower UVB range than α-tocopherol once absorbed into the skin [34].

Studies involving hairless mice given topical applications of d-α-tocopherol showed a decrease in edema, erythema and skin sensitivity, whereas pre-treatment with 5% tocopherol before UVB exposure demonstrated a 75% decrease in the severity of skin wrinkling and a significant decrease in the formation of skin tumours. However the 5% tocopherol pre-treatment demonstrated no beneficial protective effect from skin exposed to UVA. Vitamin C should be included in formulations containing vitamin E, not only for its contributing effect but also to stabilise vitamin E within the formulation against UVA irradiation.

Phenolic compounds

There is increasing interest in the use of aquatic plants as a potential source of antioxidants for therapeutic uses. Marine macroalgae are a rich source of various phenolic antioxidant compounds [35-39]. These compounds exhibit a wide range of physiological properties, such as anti-allergenic, anti-artherogenic, anti-inflammatory, anti-microbial, anti-thrombotic, cardioprotective, vasodilatory, and antioxidant effects [1,36,37,40,41]. Structurally, phenolic compounds comprise an aromatic ring, bearing one or more hydroxyl substituents, and range from simple phenolic molecules to highly polymerized compounds [42].

Despite its structural diversity, this group of compounds is often referred to as "polyphenolic" compounds. Most naturally occurring phenolic compounds are present as conjugates with mono- and polysaccharides, linked to one or more of the phenolic groups, and may also occur as functional derivatives such as esters and methyl esters. Phlorotannins (Figure 4a), a group of phenolic compounds which are restricted to polymers of phloroglucinol (1,3,5-trihydroxybenzene) (Figure 4b), have been indentified in several brown algal families such as Alariaceae, Fucaceae and Sargassaceae [43,44].

In some species of brown algae, phlorotannins comprise up to 20% of the dry tissue weight and they tend to concentrate within the outer cortical cell layers, and mitotic meristematic and meiotic sporogenous tissues [45,46]. Phlorotannins purified from several brown algae have up to eight interconnected rings. They are therefore more potent free radical scavengers than many other polyphenols, and possess strong antioxidant activity, which may be associated with their unique molecular skeleton. The multifunctional antioxidant activity of polyphenols is highly related to the phenol rings present, which act as electron traps to scavenge peroxy, superoxide-anions and hydroxyl radicals [1,41].

In order to quantify the antioxidant potential of polyphenols found in different algal species, the use of a single test is insufficient to quantify

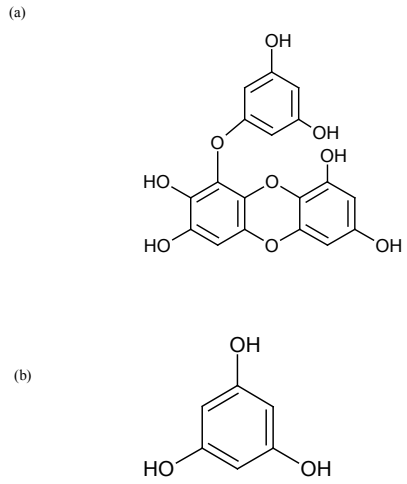

Figure 4: The structure of (a) phlorotannin and (b) phloroglucinol.

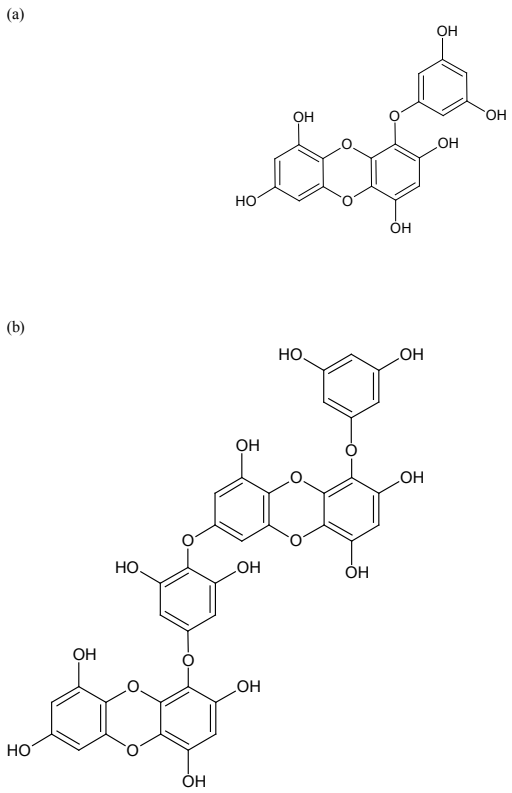

Figure 5: The structure of (a) eckol and (b) dieckol.

the different antioxidant reaction pathways involved. Therefore, in some studies three antioxidant assays, DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity, ferrous ion-chelating ability, and ORAC (Oxygen Radical Absorbance Capacity) were used to evaluate the antioxidant activity of different algae species [47-49].

In addition, phlorotannins are found to exhibit inhibitory effects on melanogenesis as well as provide protection against photo-oxidative stress induced by UVB radiation [38]. Melanin is the major pigment responsible for the color of human skin and sometimes may be over stimulated due to chronic sun exposure or other hyperpigmentation diseases. Tyrosinase, a copper-containing mono oxygenase, is a key enzyme that catalyses melanin synthesis in melanocytes [37]. It catalyses the hydroxylation of tyrosine into Dihydroxy Phenylalanine (DOPA) and other intermediates [38].

Thus, inhibition of tyrosinase activity or its production can prevent melanogenesis. Skin is always exposed to UV radiation from the sun and other environmental pollutants and is therefore a target of oxidative stress. It is well established that overexposure to UV radiation provokes an acute sunburn reaction, which clinically manifests itself as erythema [50]. Chronically UV irradiated skin is associated with abnormal cutaneous reactions such as epidermal hyperplasia, accelerated breakdown of collagen, and inflammatory responses. The effect of UV radiation has a strong oxidative component and photo-oxidative stress has been directly linked to the onset of skin photodamage [51]. Hence, regular skin treatment with products containing antioxidant ingredients is thought be a useful strategy for preventing/reducing UV induced damage (Figure 5a).

The inhibitory effect of phlorotannins on melanin synthesis (melanogenesis) and their protective effect against photo-oxidative stress induced by UVB radiation were studied using phlorotannins isolated from the brown algae, *Ecklonia cava* [30,48]. Three kinds of phlorotannins from *Ecklonia cava*, including phloroglucinol, eckol and dieckol, were isolated in order to evaluate their effects on melanogenesis and cell damage caused by UVB radiation. To evaluate whether phlorotannnins provide protection against UVB radiation, DNA damage induced by UVB radiation on cultured human fibroblast cells was measured via a comet assay on *E. cava* and presented as percent fluorescence in damaged tail.

The microscope cell images revealed comet-like shapes, indicating the DNA had migrated out from the head to form a tail (damaged DNA). The UVB radiation-induced DNA damage in cultured human fibroplast cells was reported as 51.5%. However, the DNA damage was reduced by the addition of phlorotannins to cells exposed to the UVB radiation [41]. Dieckol (Figure 5b) was shown to inhibit cellular pigmentation more effectively than kojic acid, a commercial tyrosinase inhibitor, but was much less effective than melanin synthesis inhibitor (retinol). Moreover, dieckol (the hexamer of phloroglucinol) had greater activity than eckol (trimer) and phloroglucinol (monomer). Therefore, dieckol from *E. cava* presented strong tyrosinase inhibitory and melanin synthesis inhibitory activities. Hence, dieckol may be useful as a natural whitening agent [36-38,49].

Oxidative stress may be induced by increasing the generation of ROS and other free radicals. UV radiation can also induce the formation of ROS such as singlet oxygen and superoxide anion in the skin, promoting biological damage in exposed tissues via iron-catalyzed oxidative reactions [51]. Phlorotannins were also found to exert a ROS scavenging effect. The effects of phlorotannins on cell viability in UVB radiation-induced fibroblasts were measured via a MMT assay [38,52] and were shown to exhibit inhibitory effects on intracellular oxidative damage induced by UVB radiation, with antioxidant activities associated with an improvement in cell viability [38].

These studies focused on the antioxidant activity of pholorotannins in brown algae in relation to their protection of skin from UV irradiation. Recent studies have demonstrated that the protective effect against oxidative stress induced by ROS and UV radiation is connected to the number and position of hydrogen-donating hydroxyl groups on

the aromatic ring of the phenolic molecules, and is also affected by the other factors, such as other H-donating groups (-NH, -SH). Therefore, since dieckol has more hydroxyl groups than other phlorotannins it should be effective as an anti-oxidant for use in cosmeceutical products [1,40,49].

Polysaccharides

Fucoidans: Many different types of macroalgae and marcoalgal blends have been used in cosmeceutical formulations for many decades due to their emollient, viscosity controlling and skin conditioning properties, as well as their inherent stability, bioactive properties, physical and natural marine source [53]. One such group of compounds that is showing promise for use in cosmeceutical products are fucoidans. Fucoidan or 'fucan' is a type of highly branched polysaccharide with substantial percentages of L-fucose, is generally sulfated and acetylated [54], and is mainly found in various species of brown algae (Phaeophyta) such as *Laminaria japonica, Fucus vesculosus, Undaria pinnatifida, Cladospiphon okamuranus,* and *Hizikia fusiforme.*

Conchie and O'Neill found the main component unit was 1,2-α-fucose with most of the sulfate groups located at position C-4 of the fucose units [55,56]. In 1993, using GC/MS methylation data, Patankar et al revised this structural model suggesting that the core region of fucoidan was primarily a polymer of α-(1→3) linked fucose with sulfate groups substituted at the C-4 position on some of the fucose residues [57]. Fucose was also attached to this polymer to form branched points, one for every 2-3 fucose residues within the chain (Figure 6) [58].

Of particular interest to the cosmeceutical industry are the fucoidan extracts of *F. vesiculosus*. When purified, they can be incorporated into creams and lotions, providing cosmetic anti-aging and anti-wrinkle benefits, such as inhibition of matrix enzymes against hyaluronidase, heparanase, phospholipase A2, tyrosine kinase and collagenase expression, and anti-inflammatory activity. It also was found to increase the number of dermal fibroblasts and deposition of collagen, collagen tightness and facial elasticity. As such, it demonstrates soothing, smoothing, emollient and skin conditioning properties [59].

Traditionally, the extraction of fucoidan has relied on ethanol precipitation and high temperatures, resulting in extracts with unpredictable molecular weights and solvent residues. A newer and more efficient method involves a solvent free coldwater process which yields extracts with defined molecular weight ranges and high levels of purity [60]. Currently, skin care products using fucoidan are generally composed of a partially hydrolyzed fucoidan in a base. Partially hydrolyzed fucoidan are usually extracted from heated algae. The enzymatically decomposed products of *Kjellmaniella crassifolia*, a type of brown algae, contains various forms of fucoidan including sulfated

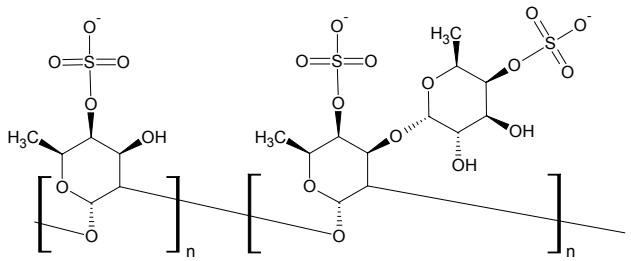

Figure 6: Patankar model for the average structure of fucoidans.

fucan, sulfated fucoglucuronomannann, and sulfated fucogalactan, all of which are used as cosmetic materials [53].

Epidemiological and experimental studies have suggested that fucoidan has particularly useful skin protecting, antioxidant, and anti-aging activities, in addition to its anti-viral, anti-inflammatory, anti-coagulant, and anti-tumor properties [53]. A recent study conducted by Fujimura and co-workers demonstrated that a fucoidan extract of *Fucus vesiculosus*, promotes the contraction of fibroblast-populated collagen gels and granulation in fibroblast-populated collagen gels through increased expression of integrin molecules, contributing to its epithelizing properties [59]. A clinical study followed, in which a gel formulation with 1% of a Fucus extract was applied topically to human cheek skin twice daily for five weeks, to investigate the effect of the extract on the thickness and the mechanical properties of human skin. A significant decrease in skin thickness, together with a significant improvement in elasticity was found, when compared to skin treated a placebo gel without the Fucus extract [60].

Given that the thickness normally increases and the elasticity usually decreases with age in cheek skin, these results demonstrated that fucoidan extracted from *Fucus vesiculosus* has anti-aging activity beneficial for aged skin. Also, it was shown that fucoidan extract aids in the promotion of collagen gel contraction. Such contraction is said to be caused by an increased expression of cell surface integrins, which mediate interactions between fibroblast and extracellular matrix proteins in the dermis.

These results therefore suggest that fucoidan may alter the thickness and the mechanical properties of skin, by enhancing integrin expression of skin fibroblasts [60]. Hence, this study demonstrates the potential usefulness of *Fucus vesiculosus* extract in a wide variety of cosmetics due to its effects on skin tightening, anti-sagging and wrinkle smoothing. Fucoidans are also of interest due to their inhibitory effects on aging and photo-damaged skin when applied topically. Studies have demonstrated that fucoidan enhances dermal fibroblast proliferation and the deposition of collagen [61].

They inhibit MMPs, which modulate connective tissue breakdown by increasing the rate of association of MMPs with their specific Tissue Inhibitors of Metalloproteinases (TIMPs). Fucoidan also minimizes elastase activity, resulting in the protection of human skin elastic fiber network against the enzymatic proteolysis [59]. Likewise, tyrosinase, an enzyme that catalyses the oxidation of phenols, is said to be inhibited by fucoidan fractions, indicating potential for it to function as a whitening agent in cosmeceuticals [62].

Fucoidan is also an effective inhibitor of chemokine receptor type 4 (CXCR4), critical regulators of cell migration in the context of immune surveillance, inflammation and development, and inhibits the accumulation of eosinophils in models of allergic skin inflammation. When compared to its mammalian analogue, heparin, fucoidan has greater potential for use as a topical anti-inflammatory for cosmetic after sun products, allergic skin condition soothing products or specialty postsurgical products, to inhibit eosinophilia due to its greater stability [63].

Moreover, since fucoidan is considered to be a dietary fiber and found to be nontoxic in cell culture, it is considered safe for inclusion into cosmeceutical products [54]. Safety trials in cancer patients demonstrated that ingestion of up to 6 g per day of *Undaria* containing 10% w/v fucoidan has no observable side effects and hence can be considered safe for therapeutic use [60]. Fucoidan can be easily incorporated (dispersed) into cosmeceutical formulations. It is water

soluble and forms relatively non-viscous solutions in water or dilute salt solutions. Hence, unlike alginates or agar, it does not add significant body to formulations. Bioactivity for fucoidan may occur in the 1 mg/ml range, indicating suitable formulation concentrations at around the 0.1% w/v-1% w/v level, depending on other factors such as molecular weight [59].

Agar: The other important compound from algae that has widespread use in the food and cosmetic industries is agar. Agar is the generic name for algal galactans containing α(1→4)-3,6-anhydro-L-galactose and β(1→3)-D-galactose residues with a small amount of sulfate, typically up to 6% (w/w). This polysaccharide hydrophilic gum is mainly extracted from the Rhodophyceae. It is, along with other polysaccharides, the main structural component of algal cell walls and has excellent gelling, viscosifying and emulsifying properties.

These desirable properties have resulted in algae being extensively used as an excipient in a wide range of pharmaceutical products (e.g. bulking agents, laxatives, suppositories, capsules, tablets, and anticoagulants). Polysaccharides have also been shown to exhibit antioxidant, antiviral, anticoagulant and antitumor properties [35,64] but these properties have not been widely made use of in commercial products. For instance, a study has reported that the lipid-soluble fraction of *Gelidium amansii*, an edible red alga, induced apoptosis of cancer cells *in vitro* [65].

Carrageenan: Carrageenan is a generic name for a family of hydrophilic polysaccharides with extremely effective thickening and gelling properties. It is used in numerous health and beauty products to provide texture and consistency. Carrageenan is a sulphated galactans and is obtained by extraction from *Chondrus crispus* (Irish moss), a species of red algae (Rhodophyta), and closely related species, *Gigartina, Eucheuma* and *Hypnea*. Carrageenan's ability to thicken or to form gels may be related to their localization in the plant cell walls, mostly in rhizomes and roots, indicative of a possible relationship with the absorption of nutrients and of a possible structural function.

The occurrence of sulfated galactans in marine organisms may be the result of physiological adaptations, not correlated to phylogenetic proximity. Sulphated galactans are classified according to the presence of the 3,6-anhydro-bridge on the 4-linked-galactose residue, and the position and number of sulphate groups [66]. They mainly consist of alternating 3-linked β-D-galactopyranose (G-units) and 4-linked α-D-galactopyranose (D-units) or 4-linked 3,6-anhydro-α-D-galactopyranose (DA-units), forming the disaccharide repeating unit of carrageenans.

The sulphate groups are covalently coupled via ester linkages to the carbon atoms C-2, C-4 or C-6 of individual galactose residues. The amount of–SO_4-in sulphated polysaccharides can be considerable and varies in the range of 0-41% (w/w), resulting in highly negatively charged polymers [67]. Due to their superior gelling and high viscosity properties, native carragenan is usually utilized in the form of their oligosaccharides.

Oligomers of carrageenan can easily be prepared through depolymerisation either by chemical or enzymatic hydrolysis. These polysaccharides are traditionally split into six basic forms: Iota (ι)-, Kappa (κ)-, Lambda (λ)-, Mu (μ)-, Nu (ν)- and Theta (θ)- carrageenan. Kappa, Iota and Lambda -carrageenan have one, two and three sulphate ester groups per two sugar units respectively, resulting in respective calculated sulphate contents of 20%, 33% and 41% (w/w). Calculated sulphate contents are based on an ideal structure.

However, carrageenans are not ideal structures and each carrageenan may have different quantities of sulphate esters at different positions and with different distributions [66,67]. Carageenan's water solubility and gel viscosity is highly dependent on its sulphate contents (very hydrophilic) and the main ionisable cations (sodium, potassium, calcium and magnesium) present [66].

The viscosity of lambda carrageenan gels (Figure 7) can be modified via interaction between the linear chains due to an increase in macromolecules (with charged particles) [66]. However, the presence of salts, lower the viscosity of carrageenan solutions by reducing electrostatic repulsion among the sulphate groups. Increased viscosity of carrageenan gels particularly for kappa, iota and hybrid kappa-2 carrageenan at low temperature and high salt concentration can be a result of "cross linking" of the chains [66,68]. An increase in temperature will decrease viscosity of these gels. This is reversible provided it is done at an optimum pH of 9 and heating is not prolonged to the point where significant thermal degradation occurs.

A particular advantage of carrageenan gels is that they are thixotropic, that is their viscosity decreases under shear stress and then returns to its original value once the stress is removed [69]. The presence of divalent cations also decreases the viscosity of these gels when present at high concentration [66,68]. Carrageenan has excellent physical functional properties and has been extensively used in the food, pharmaceutical and cosmetic industry as a gelling, thickening and protein-suspending agent.

It can produce a range of textures for creams, lotions, sticks, sprays, and foams [7]. The cosmetic industry depends heavily on carrageenan in commonly used products such as soaps, shaving foams, and body lotions. Its inclusion in these products relies on carrageenans ability to emulsify oil and water preparations and yet allow them to be easily removed with water [70].

Carageenan has a range of biological properties and has been used for a long time as an agent for the induction of experimental inflammation and inflammatory pain. It has also shown several potential pharmaceutical properties including antitumor, immunomodulatory, antihyperlipidemic, and anticoagulant activities. Some studies suggest that it might also have antiviral properties, as it inhibits the replication of herpes and hepatitis A viruses. Also, more recently it has been demonstrated that carrageenan is an extremely potent infection inhibitor of a broad range of genital Human Papilloma Viruses (HPVs), and there are indications that carrageenan-based sexual lubricant gels may offer protection against HPV transmission [66].

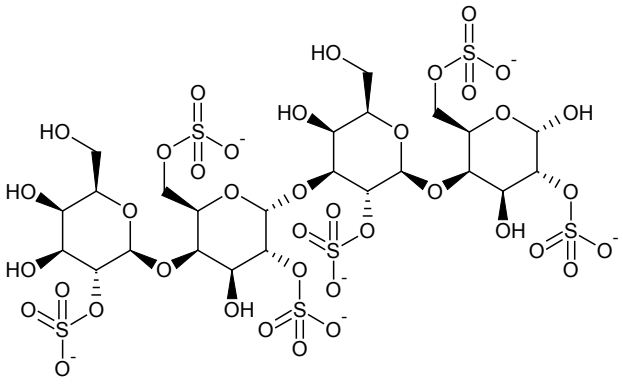

Figure 7: Lambda carrageenan.

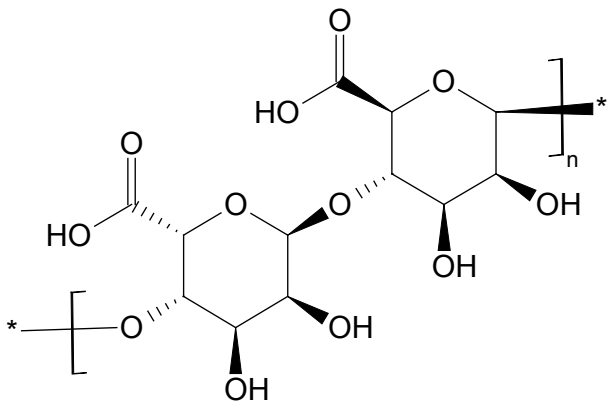

Figure 8: Alginic acid.

Alginates: Alginic acid (Figure 8) and the alginate salts, are polysaccharides and are the structural components of the cell wall of brown algae (Phaeophyceae), mainly *Laminaria* species (*Laminaria hyperborean, Laminaria digitata, Laminaria japonica*) and also *Macrocystis pyrifera, Ascophyllum nodosum, Eclonia maxima, Lessonia nigrescens, Durvillea antarctica,* and *Sargassum* spp., which are found in coastal waters around the world [60,69]. Alginate, a carboxylic polymer, comprises up to 40% w/w of dry matter from brown alga. These polysaccharides provide the algae with mechanical strength and flexibility and let them adjust to a range of water movements in which they grow. Alginates also allow them to swell in water and preserve hydration [71].

Alginates are linear unbranched polymers of α-(1→4)-linked L-guluronic acid (G) and its C5 epimer β-(1→4)-linked D-mannuronic acid (M) arranged as homopolymeric G blocks, M blocks, alternating GM or random heteropolymeric G/M stretches. Although these residues only differ at C5, they possess very different conformations; D-mannuronic acid being $^4C_1$ with diequatorial links between them and L-guluronic acid being $^1C_4$ with diaxial links between them. The proportion as well as the distribution of the two monomers determines to a large extent the physiochemical properties of alginate.

The M/G composition will vary from one species of brown alga to another. Bacterial alginates are additionally O-acetylated on the 2 and/or 3 positions of the D-mannuronic acid residues. The bacterial O-acetylase may be used to O-acetylate the algal alginates and increase their water binding [72]. Alginates rich in mannuronic acid form soft, flexible gels, with added elasticity and low porosity, whereas those which are rich in guluronic acid form firmer rigid gels with high porosity. Large quantities of mannuronic acid are found in the brown algae *Durvillea* and *Ascophyllum* whereas *Laminaria hyperborean* contains large amounts of guluronic acid [7].

Partial acid hydrolysis was used by Haug and colleagues to split alginate into three types of blocks: alternating M and G blocks; blocks of GG; and blocks of MM [71]. It was shown that rigidity of the chain increased in the order MG<MM<GG with a corresponding increase in viscosity observed for these alginates in gel form. Mannuronic acid-rich and guluronic acid-rich alginates were studied using x-ray diffraction and showed that homopolymeric blocks of the guluronic residues exist in the $^1C_4$ conformation while mannuronic residues exist in the $^4C_1$ conformation [73].

Alginate has all four probable glycosidic connections: diequatorial (MM), diaxial (GG), equatorial-axial (MG), and axial-equatorial (GM). The diaxial connection in G-blocks produces a bulky, hindered rotation around the glycosidic linkage that might explain the rigid and extended character of the alginate chain in turn making it more soluble at low pH [74].

The extraction procedure of alginate from brown algae consists of five steps: acidification, alkaline withdrawal, solid/liquid division, precipitation, and aeration [75]. The algae are cleaned, ground and then extracted using sodium carbonate. Sodium or calcium chloride is added to the filtered extract creating a tough precipitate of sodium or calcium alginate. Treatment with dilute hydrochloric acid is used to convert the alginate salt into alginic acid. The alginate is then dried and pulverised in diverse ionic forms after a series of purification steps [71].

Historically, alginate has been used extensively in the food industry as a stabiliser, emulsifier, and gelling agent. Alginate is also used in the textile/paper-printing industry as a shear-thinning agent. In medical applications it is used as an excipient in pharmaceutical products, as a dental impression material, and in wound dressings [74]. The multifaceted membranes of alginate wound dressings produce accelerated healing, which is probably associated with the hydrophilicity of alginate. Alginate has recently been used for the regeneration of cartilage, bone, nerve and liver, and for improvement of capillary blood vessels in cell culture, cell transplantation and tissue engineering [71].

Alginates have also been widely employed in cosmetics as a foundation for face masks, applications for the body, and as a broad-spectrum body wash ingredient. They are a valuable component in cosmetics due to their role in repairing skin structure and function [76], their outstanding capacity to preserve water and, and their desirable gelling, viscosity enhancing and stabilising characteristics [77]. Alginate's solubility and water-holding capacity depends on pH (precipitating below about pH 3.5), molecular weight (lower molecular weight calcium alginate chains with less than 500 residues showing increasing water binding with increasing size), ionic strength (low ionic strength increasing the extended nature of the chains), and the nature of the ions present.

At low pH, alginates are extremely efficient hydrocolloids that are used to solidify and stabilise emulsions [7]. Due to its linear molecular arrangement and high molecular weight, alginates form strong films and good fibres in the solid state [71]. A gel network is formed by the selective cross-linking of two G-blocks of adjacent polymer chains with multivalent cations (e.g. Ca^{2+} or Ba^{2+}) through the interaction of the carboxylic groups in the sugars [74]. Alginates also form acidic gels stabilised by hydrogen bonds at low pH. The stability of the gels is determined by the relative content and length of the G-blocks. It was shown that as molecular weight increases up to a maximum of roughly M_w=3×10^5 g mol^{-1}, gel strength increases [71]. Alginic acid and its calcium salt (calcium alginate) are water-insoluble. However they can swell and absorb more water than several hundred times its weight. Alginic acid is used as a thickening agent, forms a moisture-retaining surface film, and can bind heavy metal ions which are involved in oxidative processes and the formation of radicals.

A slightly tightening effect is also experienced during the superficial filming process. Hence, it fulfills several cosmetic functions at the same time. Alginic acid stabilizes the oil phase in emulsifier free cosmetics by increasing its viscosity. It is important to note that alginates are not absorbed into the skin. Propylene glycol alginate (E 405) is the ester of propylene glycol with alginic acid and is used like alginic acid.

The main use of the alginates are as thermally stable cold setting

gelling agents and are prepared by the addition of calcium ions with gelling occurring at much lower concentrations than for gelatin. Such gels can be heat treated without melting, although they may eventually degrade. The choice of gelling ions for alginate gel formation was also found to have significant effects on their final gel properties. In general, low molecular weight alginate, low concentration of gelling ions (like Ca^{2+}) and absence of non-gelling ions (Na^{+}) give the highest inhomogeneity [78]. High G content produces strong brittle gels with good heat stability (except if present in low molecular weight molecules) but prone to water separation on freeze-thaw, whereas high M content produces weaker more-elastic gels with good freeze-thaw behavior. High MGMG content together with Ca^{2+} ions is found to reduce shear [79].

Polyunsaturated Fatty Acids (PUFA)

Marine algae are very rich in Polyunsaturated Fatty Acids (PUFAs) [80], especially in the lipophilic extracts [81]. For example, PUFAs represent a large proportion of the total lipids in marine algae such as *Tetraselmis suecica, Porphyridium cruentum* and *Isochrysis galbana,* comprising 20.9%, 17.1% and 17%, respectively. Given that marine algae is a huge and renewable resource, containing a large number of different fatty acids, it provides a promising source of raw PUFAs for cosmetics [82]. Red, brown and green algae have distinguishing fatty acid profiles which do not depend on the geographical location of the algae. However, algal habitat conditions affect quantitative characteristics of the fatty acids. Each class of marine microalgae has a characteristic fatty acid pattern. It is proposed that uncommon acids, some typical acids, and the ratio of acids present, are useful chemotaxonomic markers [83-85].

Supporting literature has demonstrated that the use of fatty acids on the skin can have important therapeutic benefits. A number of fatty acids have a specific function in restoring the permeability barrier, and preventing scaly dermatitis and skin dehydration associated with a lack of unsaturated fatty acids in the skin [86]. Some of the PUFAs, such as linoleic acid and arachidonic acid, grouped under the term vitamin F, are necessary for growth and protection of the skin [87]. It was also suggested that a lack of these fatty acids leads to cutaneous problems such as alopecia, peeling of the epidermis and eczema. This is why vitamin F is incorporated at a concentration of about 5% into dermatological creams. Other PUFAs that have shown promise for use in cosmetics are omega 3 and omega 6, both of which are known to facilitate cell regeneration and skin health. In addition, PUFAs were shown to play a protective role against free radicals known to have an aging effect on skin [86].

It is important to note that the effects of PUFAs from algae on skin have not been thoroughly investigated. One study has demonstrated that two PUFAs, stearidonic acid and eicosapentaenoic acid extracted from *Undaria pinnatifida* had anti-inflammatory activity while one PUFA, arachidonic acid, extracted from *Undaria pinnatifida* had pro-inflammatory activity. The study demonstrated that stearidonic acid, inhibited leukotriene production in inflammation and was reported to act as a 5-lipoxygenase inhibitor [88,89]. Eicosapentaenoic acid was also found to suppress inflammation and its use was associated with a reduction in arachidonic acid levels [90]. These findings were supported following an experiment on mice where ear inflammations induced by arachidonic acid and UVB irradiation were significantly suppressed in mice using a dose of 300 mg eicosapentaenoic acid per kg body weight per day for 2 weeks [91].

It also demonstrated that both stearidonic acid and eicosapentaenoic acid inhibit UV induced dermal fibroblasts [53], leukocyte endothelial interactions, and inflammatory mediator release in the blood and splenocytes of mice [92]. Supplementing with 50-100 μg/mL omega-3 PUFAs, reduces the expression and activity of aggrecanases and inflammation-inducible cytokines (interleukin-1R and tumor necrosis factor-R) and cyclooxygenase-2 [93]. This work involving the therapeutic use of stearidonic acid and eicosapentaenoic acid derived from *U. pinnatifida*, support the claims that the algae can be used as a remedy for inflammation related symptoms, however further investigation is required to establish its efficacy [94].

Most of the PUFAs have good antioxidant activities [95]. 16 species of seaweeds collected along the Qingdao coastline were screened and evaluated for their antioxidant activities using the β-carotene-linoleate assay system [96]. Lipophilic extracts of all selected seaweeds exhibited various degrees of antioxidative efficacy in each screen. The highest antioxidant capacities among the tested samples were observed for *Rhodomela confervoides* and *Symphyocladia latiuscula* and were comparable with that of the well-known synthetic antioxidant butylated hydroxytoluene, and greater than that of propyl gallate. Hence, given that algae is an abundant source of PUFAs, their use in cosmeceuticals as a source of natural antioxidative compounds with therapeutic activity shows great promise.

Mycosporine-like amino acids

Mycosporine-like amino acids (mycosporine-glycine) (MAAs) are a group of over 20 UV absorbing compounds that are present in a diverse range of marine organisms where they act as sunscreens to reduce UV induced damage. Their main role is in screening against energetic UV radiation. However, MAAs also play a role in protecting against sunlight damage by acting as antioxidant molecules which scavenge toxic oxygen radicals [97]. Furthermore they act as compatible solutes to protect cells against salt stress, against desiccation or thermal stress and as intracellular nitrogen reserves [98].

MAAs are secondary metabolites found in a variety of marine algae and consist of either a cyclohenone or cyclohenimine chromophore conjugated with an amino alcohol group or nitrogen subgroup of an amino acid. They generally have a very high absorption of UV radiation between 310 and 360 nm. In a study involving murine models, the MAA Porphyra-334 (P-334) (Figure 9) and Shinorine (SH) were isolated from red alga *Porphyra rosengurttii,* and tested for their photoprotective behaviour [99]. They were shown to be very photostable, without generating any reactive intermediates such as radicals when exposed to radiation.

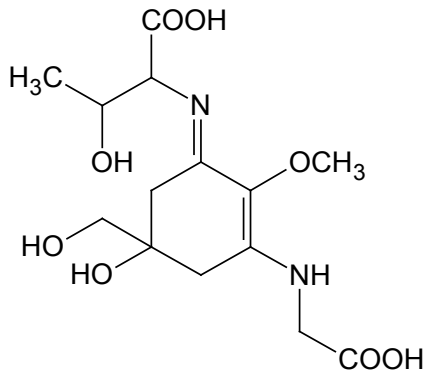

Figure 9: Mycosporine-like amino acid Porphyra-334.

In vitro, when P-334 and SH in combination were formulated in an oil/water emulsion, they exhibited broad UV spectrum protection. Topical application of this formula demonstrated prevention towards erythema, oedema, the expression of HSP 70 (heat shock proteins which are released as a protective mechanism against heat stress) and antioxidant enzyme damage. Sun Burn Cell (SBC) formation is believed to be a protective mechanism after exposure to UV radiation and eliminates cells that have become damaged. It was observed that treatment with the combination of P-334+SH treatment prevented SBC formation in UV exposed skin, hence demonstrating the DNA protective effects of MAAs when topically applied. This combination of MAAs used in treatment also demonstrated prevention towards skinfold thickening in the epidermis, dermis and hypodermis of mice. Skinfold thickening was used as an indication for actinic damage, as the degree of thickening is proportional to the quantity of radiation absorbed into the different skin layers when exposed to UVA and UVB.

The expression of HSP70 is believed to be an early repair mechanism that limits the appearance of irreversible cell injury. The study demonstrated that over expression of HSP70 was not sufficient to prevent the appearance of UV induced cell damage in non-photoprotected subjects. However, when the mice were pretreated with the combination of P-334+SH there was a slight and gradual increase in HSP70 expression with a return to baseline after 72 hours. HSP70 was considered to be an indicator of UV skin damage [100].

Conclusion

Traditionally, terrestrial plants have been the main source for new excipients/actives in skin care products. However, cosmetic scientists are beginning to focus their attention to the marine world as an additional source of novel and useful natural products. When compared with their terrestrial counterparts, most marine derived secondary metabolites are structurally more complex with unique functionalities.

Bioactive Component	Potential Function as Cosmeceutical	Other Uses
Terpenoids	Photo-damage, photo-aging	
Carotenoids	UV filter, epidermal cells renewal, antioxidant, control of cutaneous bacterial flora	
Tocopherol	UV protection	
Phenolic compounds	UV protection	
Fucoidans	Anti-aging, anti-wrinkle	Anti-viral, anti-inflammatory, anti-coagulant, anti-tumour
Carageenans	Gelling and thickening	Anti-tumour, anti-coagulant, immunomodulatory, anti-hyperlipidemic, induction of experimental inflammation and inflammatory pain, anti-viral
Alginates	Face masks & body washes, skin repair, skin hydration, gelling, stabiliser	
Agars	Gelling, emulsifying	Bulking agent, laxative, anti-coagulant, antioxidant
Unsaturated Fatty Acids	Anti-aging, UV filters, anti-wrinkle, regeneration, skin hydration	Anti-inflammatory
Mycosporin-like Amino Acids	UV filters	

Table 1: Cosmeceutical application of compounds derived from marine algae.

This is due in part to the differences in the physicochemical nature of the sea environment where conditions of high pressures, low temperatures, lack of light, and high ionic concentrations present may lead to the biosynthesis of highly functionalized and unusual molecules in marine organisms. A number of compounds from marine algae with unique beneficial skin properties have been reported (Table 1). Terpenoids, carotenoids, tocopherol, polysaccharides, phenolic compounds, mycosporine-like amino acids, and unsaturated fatty acids derived from marine algae have been found to have antioxidant properties, be UV protective, or an inhibitory effect on melanogenesis, as demonstrated by a number of *in vitro* studies.

Some compounds found in algae have not been fully investigated in relation to their cosmeceutical benefits, but current evidence shows that many of them may have an increasingly important role to play in the future development of cosmeceutical products. With the increasing demand and drive for the development and production of more effective and innovative cosmeceuticals that battle the appearance of aging, the properties of many of the compounds found in marine algae deserve further investigation.

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