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The Potential of Marine Resources in Cosmetics

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Abstract

The Ocean is a continuous body of saltwater that covers more than 70 percent of the Earth's surface. Despite the fact that oceanic habitats exhibit chemical and physical properties that make certain ocean zones suitable or unsuitable places for different species to live, the chemical (salinity and dissolved gases) and physical (temperature, density, buoyancy, waves, tides, and currents) properties of ocean water are delicately intermingled which produce one of the most self-sustaining life support systems on earth. This unique characteristic has made the marine environment an untapped source of bioactive natural products with unique structural and chemical features. Although many marine-derived compounds have been explored for their potential in pharmaceutical industry and some of which are already on the market, these molecules are still underexplored for natural cosmetics when compared to plant-derived compounds. However, recently many cosmetic firms have turned their attention to the sea to obtain several kinds of marine-derived compounds for cosmetic ingredients such as moisturizer, anti-ageing, photoprotection and skin whitening agents. With more research on the small molecules, biopolymers and enzymes from the marine environment, it is expected that the era of "blue cosmetics" will be dominating this sector very soon.

Key Words: Marine-derived compounds, moisturizer, anti-ageing, photoprotection, whitening agents, anti-tyrosinase, blue cosmetics

1. Introduction

The potential of marine natural products has captivated many researchers over the years. Inspired by the vastness of our oceans, and almost incomprehensible level of biodiversity in the marine environment, researchers have enthusiastically pursued the pharmacological potential of secondary metabolites from marine organisms. The marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural/chemical features not found in their terrestrial counterparts. Because of the physical and chemical conditions of the marine environment, almost every class of marine organisms exhibits a variety of molecules with unique structural features (Kijjoa and Sawangwong, 2004). In recent years, research on chemistry of marine organisms has experienced a tremendous increase due to the need for compounds possessing bioactivity and possible pharmaceutical applications or other economic useful properties such as fine chemicals, drugs, cosmetics and functional personal-care

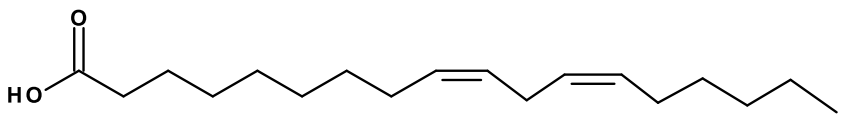
products. Despite its high level of biological and chemical diversity, the marine environment is still an underexplored resource of the discovery of novel products.

On the other hand, with ever-increasing life expectancies in several countries around the world, the physical appearance of ageing is increasingly becoming a common cosmetic concern. Due to an increased perception of the adverse effects of synthetic products, many cosmetic manufacturers have turned to Mother Nature to look for cosmetic ingredients to satisfy both consumers and regulators. Although a majority of commercialized cosmetics continue to use plant-based ingredients (Juliano and Magrini, 2018), recently the marine environment is also being recognized as a promising source of cosmetic ingredients, due to its unrivalled biological and chemical biodiversity (Brunt and Burgess, 2018).

Although the European Commission regulation has defined "cosmetics" as any substance or mixture of substances which are put in contact with the external parts of the human body or with the teeth and mucous membranes of the oral cavity to clean, perfume, protect or change their appearance or to keep them in good condition, the research and application of cosmetic ingredients are mostly concerned with the skin. This is due to the fact that the skin is the largest organ of our body which protects the organisms from deleterious environmental (physical, chemical, microbiological) agents, and is crucial for the maintenance of temperature, electrolyte and fluid balance (Makrantonaki et al., 2012). Both secondary metabolites and marine biopolymers from marine macro-and microorganisms have been found to be valuable ingredients for cosmetic products due to their antioxidant, anti-inflammatory, anti-pigmentation activities as well as their ability to restore transepidermal water loss of the skin. Thus, in this review, the compounds and extracts of marine macro-and microorganisms which are used as ingredients for moisturizers, sun screen, and whitening agents as well as to prevent skin ageing will be discussed. Some examples of commercial cosmetics with these marine-derived ingredients will be also given.

2. Active ingredients for moisturizer

Since the skin also provides a water-impermeable barrier that prevents dehydration, maintaining the hydration rate of the skin is pivotal to preserve its integrity. Topical application of lipids is normally used to prevent skin water loss. It is well recognized that ω-6 polyunsaturated fatty acids, and especially the C-18 fatty acids, such as linoleic acid (**1**) and γ-linolenic acid (**2**) have a capacity to restore transepidermal water loss (TEWL) to normal (Ziboh and Chapkin, 1987). Thus, the formulations comprising oil-in-water emulsion containing ingredients which can retain the water in the skin are used to prevent excessive loss of water from the skin.



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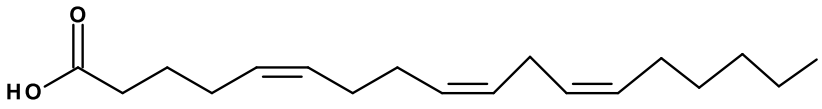

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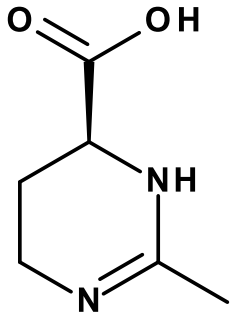
Marine algae, especially brown algae of the genus *Laminaria*, are widely used in cosmetics as moisturizers. For examples, the company Vine Vera Cosmetics commercializes the extract of *Laminaria japonica* for skin moisturizer (http://vineveragiveaway.com/benefits-of-laminaria-japonica-extract-for-skin-vine-vera-reviews/ Access on 18.11.2018). *Laminaria japonica* extract showed the strongest activity at the 2-hour mark and it was found to increase hydration by 14.44% when compared to a placebo. After the 8-hour mark, it is also capable of decreasing the transepidermal water loss (TEWL) to 20%. Another member of *Laminaria* which is used for skin care products is *Laminaria ochroleuca* whose extract is commercialized as Antileukine-6 by the firm called SEPPIC (https://www.seppic.com/antileukine-6/ Access on 18.11.2018), which is a subsidiary of the Air Liquide group in the Healthcare business. *L. ochroleuca* extract was claimed to help moisturize skin while boosting the skin's barrier layer, keeping the essential hydration. Moreover, the New Zealand-based company Xtend-life has launched skin care products containing the extract of *L. ochroleuca* as moisturizing ingredient in the hydrating facial fluid for men and soothing eye contour cream, Kanapa™ (https://www.xtend-life.com/collections/skincare/Access on 18.11.18). Besides macroalgae, the microalgae, especially of the genus *Nannochloropsis* also are found to have potential as moisturizing agent since they produce high amount of linolenic acid (Mourelle et al., 2017).

Another compound with a moisturizing property is collagen. Collagen, predominantly in the extracellular matrix, is the major structural protein of connective tissues such as skin, tendons, ligaments, and bones and accounts for about one-third of the protein of humans and three-fourths of the dry weight of skin (Chattopadhyay and Raines, 2014). Collagen is being investigated for its potential use in the biomedical field as biomaterials for biomedical or pharmaceutical applications. Collagen is also used as a moisturizer and natural humectant in cosmetic formulations (Purnamawati, et al., 2017). Collagen, which is a high-molecular weight protein, cannot be absorbed by the stratum corneum of the skin and thus remains on the skin surface and acts as a water-uptake through hydration to keep the skin moisturized (Yong et al., 2004) and as protector against microbial infiltration in cases of wounded tissue (Chattopadhyay and Raines , 2014). Although most of the collagen available in the market is extracted from the bovine and porcine by-products, the risk of transmission of zoonotic diseases such as bovine spongiform encephalopathy (BSE), transmissible spongiform encephalopathy (TSE), and Foot and Mouth Disease (FMD) has hampered its use in cosmetics. Thus, alternative/innovative sources of collagen are being explored. One of the potential sources is marine fish collagen. However, as marine fish collagen-based cosmetic formulations vary in their composition and properties, species of animal, age, and catching origin, good characterization and assessment of its quality is necessary to choose the right collagen for each formulation. One of the commercial products that incorporated marine fish collagen is the anti-ageing and anti-wrinkle skin care product, also containing the carotenoid astaxanthin, from the Thailand-based firm, Giffarine (http://www.giffarinefactory.com/ access on 18 November 2018).

Another source of marine-derived collagen is jellyfish. Jellyfish contains relatively high protein (57.8%) and is made up mostly of the collagen (34.7%). Jellyfish collagen contains proline, glycine, arginine and valine in high amounts. Jellagen, a medtech and biomaterial company, based in Cardiff, Wales, has launched a manufacturing facility to allow the extraction of high-purity collagen from jellyfish for research, medical, biotech and pharmaceutical markets (https://www.europeanpharmaceuticalreview.com/ news/51664/jellagen-launches jellyfish-collagen/Access on 18 November 2018). The

exploitation of jellyfish collagen for the cosmetic industry has been encouraged in several countries. For example, the United Nations Food and Agriculture Organization is calling for the cosmetics industry to use more jellyfish in formulations as over-fishing in the Mediterranean is boosting their numbers, thereby further reducing fish stocks. Furthermore, the reduction of the resilience of fish populations caused by jellyfish feeding on fish larvae and young fish can be solved if the cosmetic industry opts to use more collagen from jellyfish (https://www.cosmeticsdesign.com/Article/2013/06/03/Cosmetics-industry-use-of-jellyfish-can-help-falling-fish-stocks-to recover?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright./Access on 18 November 2018]. The French company Eficience has launched several cosmetic products containing jellyfish collagen, including intensive lifting serum (http://eficience-saintbarth.com/index-english-version.html/Access on 18.11.18).

Compounds produced by bacteria were also found to have a potential as moisturizing agents. Bacteria, especially those living in extreme environments, have the ability to produce compounds of small molecular weight, known as osmoprotectants. These compounds strongly bind water molecules and stabilize macromolecules but do not interfere with cellular processes. One of these compounds is ectoine or 1,4,5,6-tetrahydro-2-methyl-4-pyrimidine carboxylic acid (**3**), which is a water binding zwitterionic amino acid derivative, first isolated from *Ectothiorhodospira halochloris* but also produced and accumulated by other, mainly aerobic, chemoheterotrophic and halophilic bacteria, such as alpha- and gamma proteobacteria and Actinobacteridae, in which it stabilizes cell membranes, enzymes, and nucleic acids at extreme temperatures or higher salt concentrations. Ectoine was found to have a similar capacity to bind water molecules to other osmoprotectants such as glycerol and has strong hydration property. Ectoine improved hydration of the cell surface by increasing intermolecular spacing and boosts the mobility of the lipid head groups in the cell membrane (Bownik and Stępniewska, 2016).



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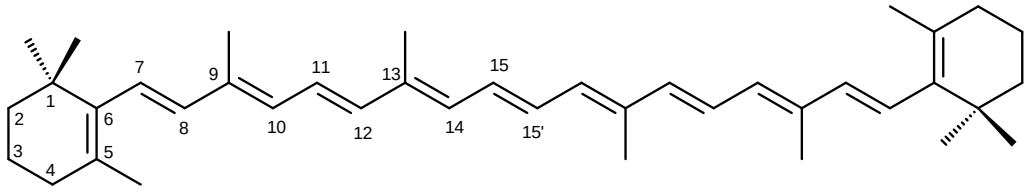
Topical application of ectoine-formulated products is well tolerated by humans and is proved to be an effective long-term moisturizer that prevents dehydration of epidermis. The German company Bitop AG which focused on the manufacturing and utilization of natural protective molecules, the so-called “Extremolytes” is commercializing several cosmetic products containing ectoine (EHK02-01) such as face cream, cream for dermatitis, allergy nasal spray, ear spray and spray for mouth and throat (https://www.cphi.com/europe/exhibitors/bitop-ag/Access on 21 November 2018).

3. Active ingredients for prevention of skin ageing

Skin ageing is caused by a degradation of extracellular matrix in both epidermis and dermal layer. Skin ageing is generally associated with the formation of wrinkles, skin laxity, and hyperpigmentation, and can commonly be categorized as a long-term damage caused by various stressors. Skin ageing is influenced by intrinsic factors (genetics, ethnicity and sex) and extrinsic factors, including exposure to UV radiations, harsh weather, pollution, smoking, stress and poor sleeping, as well as eating habit and exercise. Although the fundamental mechanisms of skin aging are still not well understood, there is an increasing evidence, which indicates the involvement of multiple pathways in the generation of aged skin. Expression-profiling studies and studies of progeroid syndromes have shown that among the most important biological processes involved in skin ageing are alterations in DNA repair and stability, mitochondrial function, cell cycle and apoptosis, ubiquitin-induced proteolysis, and cellular metabolism. Additionally, it was revealed that one of the major factors that has been proposed to play a fundamental role in the initiation of ageing is the age-related decrease of physiological hormone (Makrantonaki and Zouboulis, 2007).

Among natural products used as ingredients to prevent skin ageing, carotenoids are considered major active principles with anti-ageing properties. Within this class of compounds, β-carotene (**4**) is considered the top pigment which possesses an excellent capacity to prevent a formation of Reactive Oxygen Species (ROS). β-Carotene is also used in anti-ageing formulation as provitamin A (Grune et al., 2010). The most important marine source of β-carotene is the halotolerant microalga *Dunaliela salina* which produces more than 10% of β-carotene of its dried weight. Besides β-carotene, this microalga also biosynthesizes 9-*cis*-β–carotene (**5**), which has a considerably high antioxidant activity and helps heal damaged skill cells in addition to fighting infection (Raja et al., 2007).

Besides these two carotenoids, *D. salina* also contains a large number of minerals such as magnesium, potassium, calcium, in addition to glycerin and iodine due to the environment where it grows. These minerals can stimulate the relaxation and repairment of stressed skin tissue. They also help protecting the skin cells from free radicals. These properties make *D. salina* extract an important ingredient in cosmetic products for protecting and refreshing sensitive skin.



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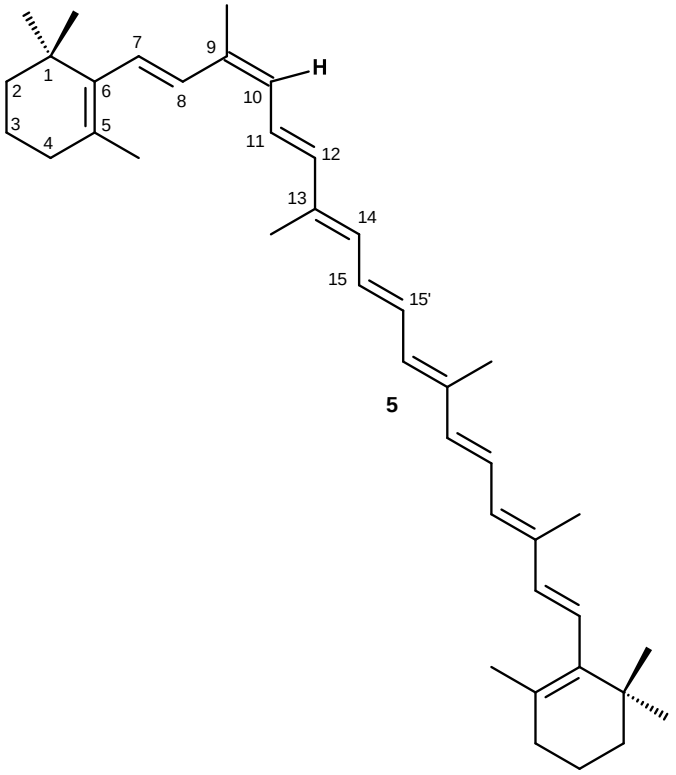

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Another class of anti-ageing compounds is polysaccharides. Alguronic acid is a tradename coined by Solazyme (now TerraVia Holdings, Co.) for an undetermined mix of polysaccharides produced by a unique strain of microalgae. Alguronic acid is a powerful regenerative compound produced by microalgae that functions to protect and regenerate them in harsh environmental conditions. In 2011, the firm called Algenist introduced alguronic acid to the market, as an active ingredient in a commercial product for anti-ageing skincare formulas. Algenist claimed that alguronic acid minimizes the appearance of wrinkles, improves the appearance of skin firmness and delivers smoother, more radiant looking skin (https://www.algenist.com/pages/technology/ Access on 20 November 2018). In recent years, there has been a growing interest in isolating bacteria from extreme environments such as deep-sea hydrothermal vents. *Alteromonas macleodii* subsp. *fijiensis* biovar deepsane, isolated from a polychaete annelid *Alvinella pompejana,* which was collected on the East Pacific Rise at 2600 m depth, was found to excrete the exopolysaccharide known as deepsane. Structurally, deepsane contains an unusual trisubstituted galacturonic acid and represents one of the most complex carbohydrate structures so far reported (Le Costaouec et al., 2012). Deepsane is commercially available in cosmetics under the name of Abyssine® by Lucas Meyers for soothing and reducing irritation of sensitive skin against chemical, mechanical and UV-B aggression.

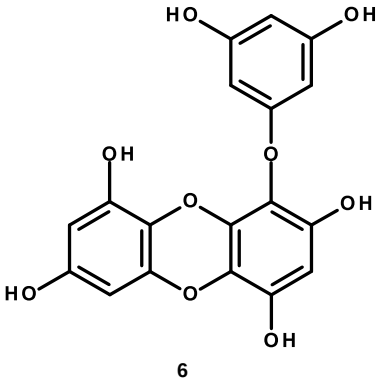
Moreover, there are other strategies for treatment to diminish symptoms of skin ageing. This includes (i) Inhibition of the degradative enzymes, collagenase and elastase, (ii) stimulation of keratin, glycoaminoglycans (GAGs), and collagens I and III synthesis, (iii) inducing hyaluronic acid synthesis, and (iv) inhibition of enzymes Matrix Metalloproteinases (MMPs). However, other treatments to lessen the symptoms of aged skin also exist, including wrinkle reduction, increased cutaneous hydration and collagen replenishment.

Alternatively, the inhibition of the degradative enzymes, collagenase and elastase, can counteract the process of ageing. For this purpose, fucoidan, obtained from the phaeophyte *Undaria pinnatifida*, was shown to inhibit bacterial collagenase and human neutrophil elastase *in vitro* while a polyphenolic extract, containing fucoidan from the pheophyte *Fucus vesiculosus*, showed significant inhibition of elastase *in vitro*. The product FIRM'ACT® of Gelyma combines two extracts prepared from the brown seaweeds *Himanthalia elongata* and *Fucus vesiculosus* with a specific extract of *Saccharomyces cerevisiae* supplemented with selenium, each one complementing another, especially in anti-oxidant properties. FIRM'ACT® is based on the concept of hormesis for fighting both intrinsic and extrinsic skin ageing through several adaptive abilities against various kinds of stress, especially oxidative stress and metals-induced stress (http://www.gelyma.com/firmact.html/Access on 21 November 2018). Another product, based on macroalgal extracts, is Slendyl® from Biosil Technologies, Inc. Slendyl® combines two brown algal extracts, prepared from *Himanthalia elongata* and *Undaria pinnatifida*, using a specific mineral spring water known for its richness in certain minerals. It acts through a global strategy based on the three main pathways of fat accumulation: adipogenesis, lipogenesis and lipolysis, with additional reinforcement of skin firmness (https://www.ulprospector.com/en/na/PersonalCare/Detail/4655/647413/SLENDYL/ Access on 21 November 2018).

Hyaluronic acid, also called hyaluronan, is an anionic, non-sulfated glycosaminoglycan distributed widely throughout connective, epithelial, and neural tissues. It is a major component of the skin extracellular matrix. Therefore, inducers of hyaluronic acid synthesis are commonly used in anti-aging care. It was shown that the extract of the giant brown seaweed *Macrocystis pyrifera,* found in the Antarctic, may stimulate the synthesis of hyaluronan and syndecan-4, another important protein of the extracellular matrix. The product called Tonikemp® of GELYMA for anti-wrinkle, collagen synthesis, DNA and skin protections, kin maintenance and tissue regeneration, contains *Macrocystis pyrifera* extract (and) hydrolyzed yeast extract (http://www.biosiltech.com/tonikelp/Access on 21 November 2018). A combination of extracts from the red algae *Meristotheca dakarensis* and *Jania rubens* is available on the market which has been described as stimulating keratin, glycoaminoglycans (GAGs), and collagens I and III synthesis. Gelyma has launched a product called Dermocea® for a plumber and firmer skin. Dermocea® contains *M. dakarensis* and *J. rubens* extracts. *Jania* is recognized for its ultramoisturizing and protective properties due to a high concentration of minerals and trace elements present in its tissue (http://www.gelyma.com/dermocea.html/Access on 21 November 2018). *J. rubens* is characterized by a concentration of minerals and trace elements 20,000 to 40,000 times greater than that of seawater, thus giving it remineralizing properties.

The enzymes matrix metalloproteinases (MMPs) are also known to be involved in the ageing process. They are Zn^{+2} extracellular endopeptidase enzymes produced by a variety of cells, including fibroblasts, keratinocytes, mast cells, macrophages and

neutrophils. They cause extensive degradation of collagen which resulted in formation of wrinkles. Therefore, searching for inhibitors of MMPs may be another avenue for anti-wrinkle cosmetic products. Several endeavors have been made to identify inhibitors of MMPs from marine resources. For examples, the polyphenols eckol (**6**) and dieckol (**7**), isolated from the seaweed *Ecklonia stolonifera* were found to inhibit the expression of matrix metalloproteinase-1 in human dermal fibroblasts (Joe et al., 2006). Therefore, the algal polyphenols can be a potential source of anti-wrinkle agents in cosmetics.



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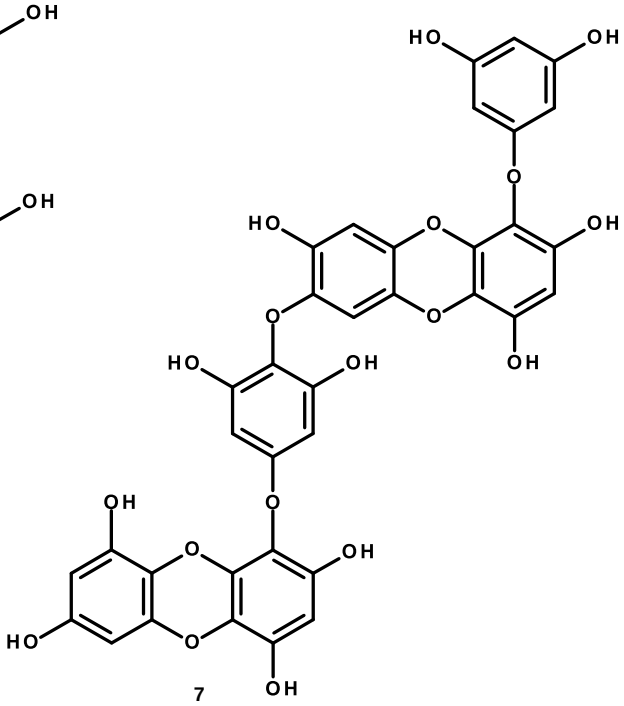

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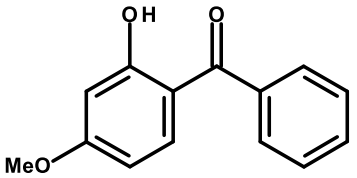
Peptides and enzymes are also valuable ingredients for anti-ageing of skin in cosmetic formulas. One of the examples is the Zonase™ enzyme, a serine endoprotease from Atlantic salmon (*Salmo salar*) eggs. Zonase™ helps the larva getting off its eggshells by digesting the tough, fibrous protein structure but without harming the delicate baby fish. The extract from the water after the hatching is finished was patented by the ABT firm as Aquabeutine XL® to use in cosmetics. Aquabeutine XL® does not contain only the Zonase™ enzyme but also unsaturated fatty acids, proteins, DNA, RNA, vitamins and minerals. The Zonase™ is used for micro-exfoliation since it mimics skin enzymes and degrade corneodesmosomes, specific cell binding sites in the stratum corneum to gently remove dead skin cells without harming the skin cells underneath. Moreover, eggshell proteins can cause a moisturizing effect by transporting and retaining moisture into the stratum corneum and replenish the skin while polypeptides stimulate the growth and the differentiation of new cells, thus furnishing rejuvenating effect for the skin.

4. Active ingredients for topical photoprotection

Skin can be damaged by chronic exposure to UV radiations. UV-A (400-320 nm) is linked to skin aging and may contribute to some form of skin cancer while UV-B (320-290 nm) can cause sunburn and skin cancer. The damage caused by this long-term effects need to be prevented by using appropriate protection such as sunscreens during

the exposure to UV radiations. There is a big concern about the health and environmental effects of current sunscreens among consumers. Moreover, lawmakers are also more likely to strict them. Some sunscreen compounds approved by the U.S. Food and Drug Administration (FDA) have recently been under investigation for their potential link to an increase of cancer risk by disrupting hormone signaling. Some of the synthetic compounds of sunscreens such as oxybenzoate (**8**) or octinoxate (**9**) were suspected to harm coral reefs (Pandika, 2018).



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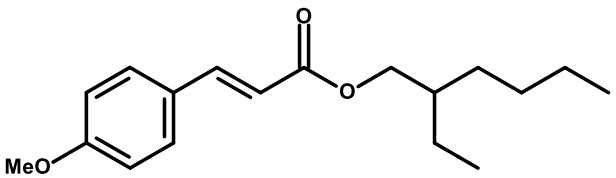

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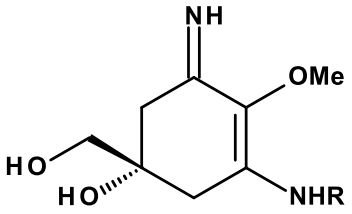
Recently, a growing number of researchers believe that photoprotective compounds from marine organisms such as algae and other photosynthetic organisms could soothe consumers'concerns and protect the environment. This reasoning is based on the fact that the photosynthetic organisms that rely on sunlight for energy also need to protect themselves from the harmful effects of UV radiations in the sunlight. Contrary to some plants which have a waxy cuticle as physical barriers that can deflect the UV radiation, marine organisms like algae that lack this physical barriers have developed chemical compounds for photoprotection to defense themselves. Several photosynthetic marine organisms are found to produce compounds that absorb UV radiations. One of the most interesting classes of these compounds are mycosporine-like amino acids (MAAs). MAAs are a family of compounds that consist of a core cyclohexinimine (**10**) or cyclohexanone ring (**11**) with various functional groups attached to the ring. MAAs can be an attractive candidate sunscreen ingredient because they are not only low molecular weight molecules but also water soluble and stable when exposed to light and heat.



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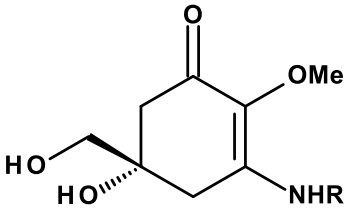

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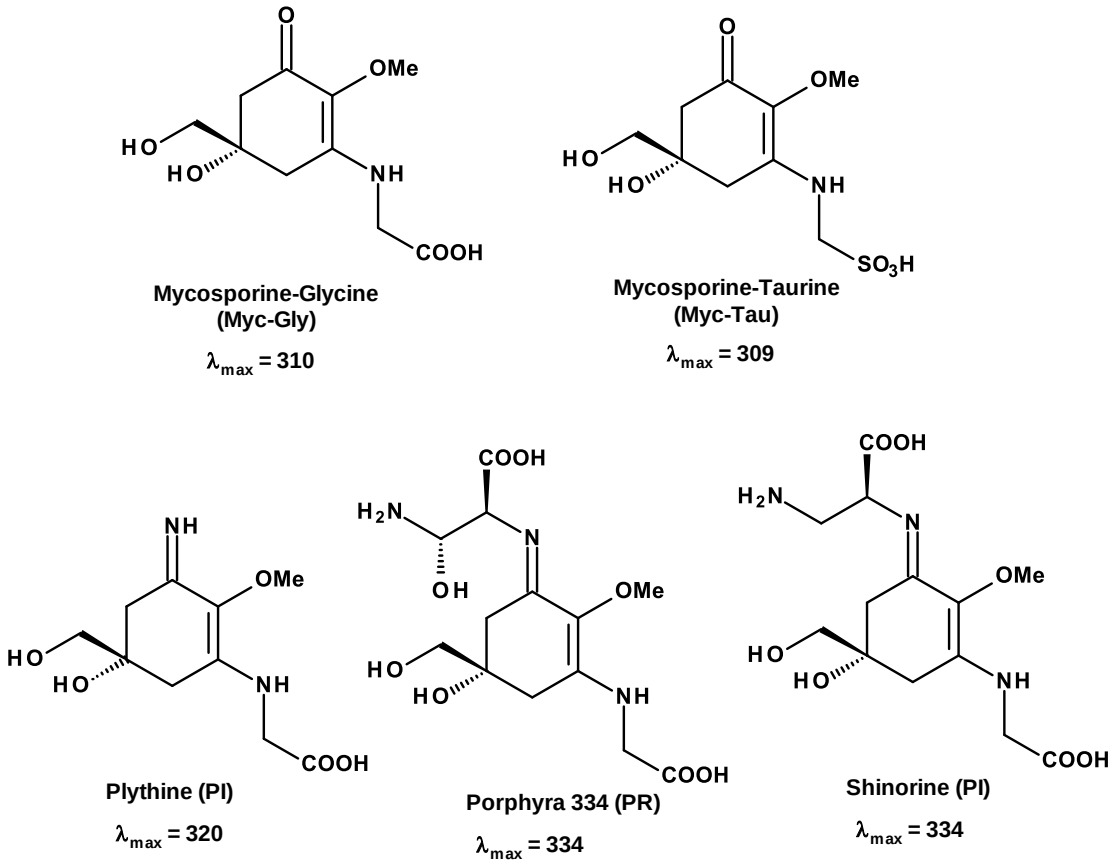
MAAs have since been found in a diverse variety of freshwater and marine organisms including cyanobacteria, macro- and microalgae, corals as well as many marine invertebrates such as sea anemones, limpets, shrimps, sea urchins and vertebrates including fish and fish eggs (Llewellyn and Airs, 2010). The conjugated double bonds in MAAs make them absorb broad band of UV radiations with the wavelength maxima (λ_{max}) ranging from 310 nm in the UV-B for cyclohexanone-based structures to 360 nm in the UV-A for cyclohexenimine based-structures. However, the substituents of the cyclohexenimine and cyclohexanone cores can change their λ_{max} (Karentz et al., 1991). Examples of some relevant MAAs and their λ_{max} are shown below:



The Mibelle AG Biochemistry Company has launched a sunscreen product called Helioguard 365® which contains porphyra 334, extracted from *Porphyra umbilicalis*(https://www.ulprospector.com/en/na/PersonalCare/Detail/2251/63465/Helioguard-365/Access on 23 November 2018] The Gelyma Company has patented water and concentrated active ingredient prepared from the same seaweed and named it HELIONORI®. The company claimed that the extract contained the MAAs palythine, porphyra 334 and shinorine (https://www.ulprospector.com/en/eu/PersonalCare/Detail/15394/365433/HELIONORI/Access on 23 November 2018). Palythine, extracted from the red alga *Chondrus yendoi*, was found to protect human skin cells, grown in the laboratory, from UV-A and UV-B damage under artificial sunlight as intense as at noon in the Arizona Summer and the researchers have filed a patent application of palythine and licensed it to a London-based skin care company, SeaLuxe, which plans to release a products containing it as the active ingredient (Lawrence et al., 2018).

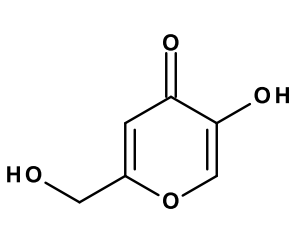
5. Active ingredients with skin whitening properties

In the Western world, a tan skin is considered as healthy and a sign of well-being and thus artificial tanning has been a blooming business throughout. On the contrary, in the Eastern World, a light complexion is assumed to be related to beauty and of high social status. Consequently, developing formulations for eliminating hyperpigmentation or to safely achieve overall whitening is a great challenge for the cosmetic industry. In recent years, the interest in skin whitening has grown tremendously since there is a great demand for whitening cosmetics for the care of lentigo, pregnancy mask, residual

hyperpigmentation or hyperpigmentation following medicine poisoning (Guillerme et al., 2017).

Skin pigmentation is caused by the melanin pigment, which is synthesized from the amino acid L-tyrosine that is converted to dopaquinone by the enzyme tyrosinase. Melanin is produced and stored inside in the melanosomal compartment of the melanocyte, which is transported to the overlaying keratinocytes. Although there are several mechanisms for preventing the melanin formation, one of the most obvious cellular targets of depigmentation compounds is the enzyme tyrosinase.

Although hydroquinone has been widely used as an effective whitening agent in cosmetic formulations, it has been banned recently due to its ability to cause mutagenicity as well as the increased incidence of ochronosis in African countries (Bhattar et al., 2015). Among thousands of compounds showing inhibitory activity on tyrosinase, only two natural compounds, kojic acid (**12**) and arbutin (**13**), have found their use as whitening agents in many cosmetic formulations



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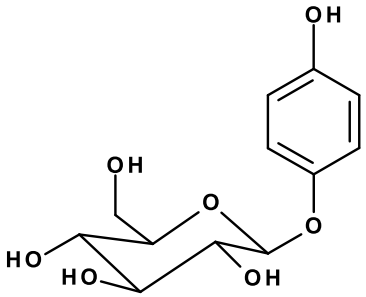

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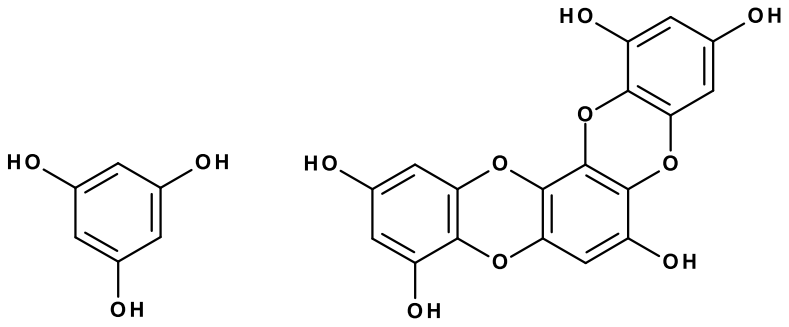
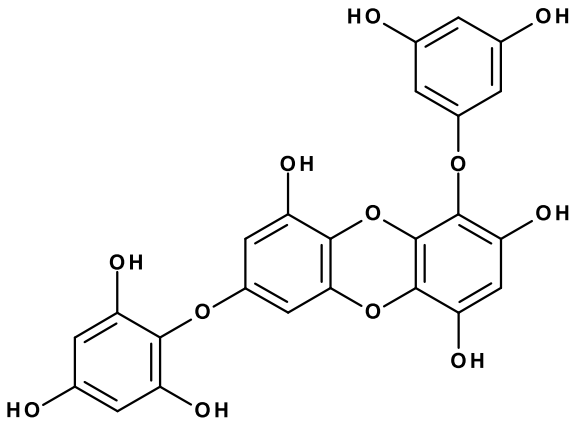
Kojic acid is produced by several species of fungi, especially *Aspergillus oryzae* (whose Japanese common name is *koji*). Kojic acid is a by-product in the fermentation process of malting rice in the manufacturing of sake. Arbutin is a glycosylated form of hydroquinone that is present in bearberry plant in the genus *Arctostaphylos*, among many other medicinal plants primarily in the Ericaceae family. Bearberry extract is used in skin lightening treatments designed for long term and regular use. *In vitro* studies of human melanocytes exposed to arbutin at concentrations below 300 μg/mL caused a decrease in tyrosinase activity and melanin content with little evidence of cytotoxicity.

In recent years, several research groups have focused on the discovery of new marine organisms as sources of skin-whitening compounds. The extract of a green microalgae *Chlorella vulgaris* extract was found to reduce skin pigmentation by more than 10%. The French company Codif has launched the product called Dermochlorella D, which contains the extract of *C. vulgaris.* Dermochlorella has been shown to stimulate collagen synthesis, decrease the morphology of stretch marks and reduce vascular imperfections (https://cosmetics.specialchem.com/product/i-codif-dermochlorella-d). The search for compounds with antityrosinase activity from the marine sources has led to the finding that the ethanolic extract and ethyl acetate soluble fraction obtained from the red alga *Ecklonia cava* had a marked inhibitory effect on mushroom tyrosinase at a concentration of 50 μg/mL. Chromatographic purification of these extracts led to the isolation of phloroglucinal (**14**), dioxinodehydroeckol (**15**) and 7-phloroeckol (**16**). 7-Phloroeckol (16) exhibited more potent tyrosinase inhibitory effect (with an IC_{50} value of 0.85 μM) than arbutin (IC_{50} = 243.16 μM) and kojic acid (IC_{50} = 40.28 μM). It was suggested that suggest that 7-phloroeckol (**16**) functioned as a noncompetitive inhibitor against tyrosinase. Treatment of the IBMX-induced melanin formation in B16F10

melanoma cells with 7-phloroeckol (6.25-100 μM) resulted in a significant inhibition of melanin production. Therefore, 7-phloroeckol might prove useful as a novel inhibitor of melanin formation in cosmetic applications. (Yoon et al., 2009).

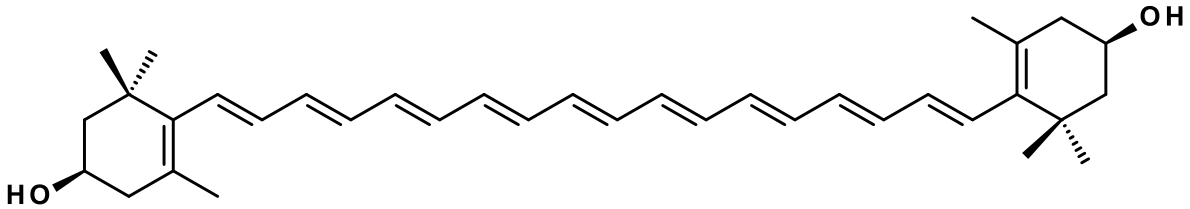


14 **15**



16

Some of microalgae can be an interesting source of antityrosinase compounds. It was found that the carotenoid, zeaxanthin (**17**) generated from the supercritical anti-solvent (SAS) process of extracting microalga *Nannochloropsis oculata*, showed antityrosinase activity in the agar plate method using the mushroom tyrosinase (200Unit/mL) (Shen et al., 2011).



17

It is interesting to point out that although numerous tyrosinase inhibitors have been identified, most of them lack clinical efficacy because they were identified using mushroom tyrosinase as a target which is different from mammalian or human tyrosinases. Man et al. (2018) have used a recombinant human tyrosinase to screen a library of compounds and compared the active screening hits with well-known whitening ingredients. They have found that kojic acid showed a weak efficacy (IC_{50} >500 μmol/L) with this enzyme.

6. Conclusion

Due to the physical and chemical conditions in the marine environment, a variety of molecules with unique structural features are produced by marine organisms. Although marine-derived molecules have attracted attention of many researchers in the past two decades, their applications as pharmaceuticals, nutraceuticals and cosmeceuticals are still underexplored. Due to consumers' concerns of the chemicals used as ingredients in various cosmetic formulations, the sector has turned to Mother Nature. Therefore, there are more and more natural products-based cosmetics on the market nowadays. Interestingly, sustainability is currently the buzz word in the cosmetic ingredients industry which goes beyond the trend natural raw materials. In this context, more and more brands of cosmetics are turning toward the sea to get a sustainable source of natural cosmetic ingredients. Despite most of research works have been performed on pure marine-derived compounds, the marine ingredients in most of the cosmetic formulations continue to be in the form of extracts. Therefore, a precise chemical characterization of the extracts and the evaluation of the mechanisms of bioactivity of the extracts need to be further explored to validate the quality of the marine-based cosmetics.

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References

Bhattar, P. A., Zawar, V. P., Godse, K. V., Patil, S. P., Nadkarni, N. J., Gautam. M. M. 2015. Exogenous ochronosis. Indian Journal of Dermatology, 60(6):537-543.

Bownik, A. and Stępniewska, Z. 2016. Ectoine as a promising protective agent in humans and animals. Archives of industrial hygiene and toxicology, 67:260-265.

Brunt, E. G. and Burgess, J. G. 2018. The promise of marine molecules as cosmetic active ingredients. International Journal of Cosmetic Science, 40: 1-15.

Chattopadhyay, S. and Raines, R. T. Collagen-Based Biomaterials for Wound Healing. Biopolymers, 101(8): 821-833.

Grune, T., Lietz, G., Palou, A., Ross A. C., Stahl, W. Tang, G., Thurnham, D., Yin, S., Hans Biesalski. 2010. K. *β*-carotene is an important vitamin A source for humans. The Journal of Nutrition, 140(12): 2268S-2285S.

Guillerme, J. B., Couteau, C., Coiffard, L. 2017. Applications for marine resources in cosmetics. Cosmetics, 4(3), 35; doi:10.3390/cosmetics4030035.

Juliano, C. and Magrini, G. A. 2018. Cosmetic Functional Ingredients from Botanical Sources for Anti-Pollution Skincare Products. Cosmetics, 2018, 5 (1), 19; https://doi.org/10.3390/cosmetics 5010019.

Joe, M. J., Kim, S. N., Choi, H. Y., Shin, W. S., Park, G. M., Kang, D. W., Kim, Y. K. 2006. The inhibitory effects of eckol and dieckol from *Ecklonia stolonifera* on the expression of matrix metalloproteinase-1 in human dermal fibroblasts. Biological and Pharmaceutical Bulletin, 29(8):1735-1739.

Karentz, D., McCuen, F.S. Land, M.C. Dunlap, W.C. 1991. Survey of mycosporine-like amino acid compounds in Antarctic marine organisms: Potential protection from ultraviolet exposure. Marine Biology, 1991, 108:157-166.

Kijjoa, A. and Sawangwong, P. 2004. Drugs and Cosmetics from the Sea. Marine Drugs, 2 (2): 73-82.

Lawrence, K.P., Gacesa, R., Long, P.F., Young, A. R. 2018. Molecular photoprotection of human keratinocytes in vitro by the naturally occurring mycosporine-like amino acid palythine. British Journal of Dermatology, 178:1353–1363.

Le Costaouec, T, Cérantola, S., Ropartz, D., Sinquin, C., Colliec-Jouault, S., Boisset, C. 2012. Structural data on a bacterial exoplysaccharide produced by a deep-sea *Alteromonas macleodii* strain. Carbohydrate Polymers, 90:49-59.

Llewellyn, C. A. and Airs, R. L. 2010. Distribution and Abundance of MAAs in 33 species of microalgae across 13 classes. Marine Drugs, 8, 1273-1291; doi:10.3390/md804127.

Makrantonaki, E., Zouboulis, C. C. 2007. Molecular mechanisms of skin aging: state of the art. Annals of the New York Academy of Sciences, 1119:40-50.

Mann, T., Gerwat, W., Batzer, J., Eggers, K., Scherner, C., Wenck, H., Stäb, F., Hearing, V. J., Röhm, K. H., Kolbe, L. 2018. Inhibition of human tyrosinase requires molecular motifs distinctively different from mushroom tyrosinase. Journal of Investigative Dermatology, 138:1601-1608.

Makrantonaki, E., Bekou, V., C. C. Genetics and skin aging. Dermatoendocrinoly, 2012 4(3): 280-284. doi:10.4161/derm.22372.

Mourelle, M. L., Carmen P. Gómez, C. P., Legido, J. L. The Potential Use of Marine Microalgae and Cyanobacteria in Cosmetics and Thalassotherapy. Cosmetics, 2017, 4 (4): 46; doi:10.3390/ cosmetics4040046.

Pandika, M. 2018. Looking to nature for new sunscreens. ACS Central Science, 4 (7), 788–790.

Purnamawati, S., Indrastuti, N., Danarti, R., Saefudin, T. 2017. The Role of Moisturizers in Addressing Various Kinds of Dermatitis: A Review. Clinical Medicine and Research, 15(3-4): 75-87.

Raja, R., Hemaiswarya, S., Rengasamy, R. 2007. Exploitation of *Dunaliella* for β-carotene production. Applied Microbiology and Biotechnology, 74:517-523.

Shen, C. T., Chen, P. Y., Wu, J. J., Lee, T. M., Hsu, S. L., Chang, C. M., Young, C. C., Shieh, C. J. 2011. Purification of algal anti-tyrosinase zeaxanthin from *Nannochloropsis oculata* using supercritical anti-solvent precipitation. Journal of Supercritical Fluids**,** 55: 955–962.

Yong, P., Glattauer, V.; Werkmeister, J. A, W., Ramshaw, J. A. M. 2004). Evaluation of collagen products for cosmetic application. Journal of cosmetic science, 55: 327-341.

Yoon, N. Y, Eom, T. K., Kim, M. M., Kim, S. K. 2009. Inhibitory effect of phlorotannins isolated from *Ecklonia cava* on mushroom tyrosinase activity and melanin formation in mouse B16F10 melanoma cells. Journal of Agricultural and Food Chemistry, 27: 57(10):4124-4129.

Ziboh, V.A., Chapkin, R.S. Biologic significance of polyunsaturated fatty acids in the skin. Archives Dermatoly, 1987, 123 (12): 1686a-1690.