Universidade de Lisboa
Faculdade de Farmácia

Natural Products applied as Innovative Cosmetic Ingredients

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Monografia orientada pela Professora Doutora Catarina Pinto Reis, Professora Auxiliar, FFUL e coorientada pela Professora Doutora Luísa Margarida Batista Custódio, investigadora assistente

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Resumo

Ingredientes naturais têm sido usados tradicionalmente por milénios e a sua aplicação em cremes tópicos, loções e preparações dentro da medicina tradicional e tradições de cura em muitas culturas têm sido observadas. Nos últimos 20 anos, estudos laboratoriais e clínicos têm identificado os benefícios de uma variedade de ingredientes naturais para cuidados de pele. Consequentemente, alguns destes ingredientes e compostos estão a ser desenvolvidos, usados ou considerados não só para efeitos anti idade, mas também para distúrbios dermatológicos. Certos ingredientes como lama marinha e quitosano, têm sido identificados como benéficos no tratamento de psoríase e dermatite atópica, devido às suas propriedades anti-inflamatórias. Para combater acne, sargafurano e

diterpenóides cembrene são considerados eficazes. Já para a hiperpigmentação e capacidades antioxidantes, florotaninos e fucoidano estão entre os compostos que se consideram mais benéficos. Pesquisa adicional é necessária para determinar, confirmar e elucidar os benefícios destes ingredientes na prevenção e controlo dos distúrbios de pele.

Palavras-chave: Marinho, cosmética, moléculas bioativas, inovação e sustentabilidade.

Abstract

Natural ingredients have been used traditionally for millennia and their application in topical creams, lotions and preparations within the traditional medicines and healing traditions of many cultures has been observed. Over the last 20 years, clinical and laboratory studies have identified the benefits of an array of marine natural ingredients for cosmetic. Consequently, a number of these ingredients and compounds are today being developed, used or considered not only for anti-aging effects, but also for use in dermatologic disorders. Certain ingredients, such as sea mud and chitosan, have been identified as beneficial in the treatment of psoriasis and atopic dermatitis, due to their anti-inflammatory properties. For combating acne, sargafuran and cembrene diterpenoids are considered efficacious. As to hyperpigmentation and antioxidative capabilities, phlorotannins and fucoidan are among those compounds found to be most beneficial. Additional research is needed to determine, confirm and elucidate the benefits of these ingredients in the prevention and management of skin disease.

Keywords: Marine, cosmetics, bioactive molecules, innovative and sustainable.

Index

Figure Index

Table Index

Abbreviations List

AP-1 - Activator protein-1
ASX – Astaxanthin
BHA - Butylated hydroxyanisole
BHT - Butylated hydroxytoluene
CAT - Catalase
COX - Cyclooxygenase
DHA - Docosahexaenoic acid
DOPA - Dihydroxyphenylalanine ECM
- Extracellular matrix
EAE - Enzyme-assisted extraction
EPA - Eicosapentaenoic acid
EPSs - Exopolysaccharides
FA - Fatty acids
FOs - Fish oils
GAG - Glycosaminoglycan
GMOs - Genetically modified organisms
GR - Glutathione reductase
GSH - Glutathione peroxidase
GST - Glutathione transferase
HA - Hyaluronic acid
HMF - High molecular weight fucoidan
LMF - Low molecular weight fucoidan
MAAs - Mycosporine-like amino acids
MAE - Microwave-assisted extraction

MAPK - Mitogen-activated protein kinases
MITF - Microphthalmia-associated transcription factor
MMP - Matrix metalloproteinase
MS - Mass spectrometry
N/A - Not available
NF-κB - Nuclear factor-κB
NMF - Natural moisturizing factor
NMR - Nuclear magnetic resonance
NSAIDs - Nonsteroidal anti-inflammatory drugs
NP - Natural products
PET - Polyethylene Terephthalate
PGE2 - Prostaglandin-E2
PLE - Pressurized fluid/liquid extraction
PUFA - Polyunsaturated fatty acids
ROS - Reactive oxygen species
SC - Stratum corneum SCOs
- “single-cell oils”
SFE - Supercritical fluid extraction
SOD - Superoxide dismutase
TAG - Triacylglycerol
TBHQ - Tert-butylhydroquinone
TPM - Tetraprenyltoluquinol chromane meroterpenoid
TLC - Thin layer chromatography
UAE - Ultrasound-assisted extraction
UV – Ultraviolet
UVA - Ultraviolet A
UVB - Ultraviolet B
WGS - Whole genome shotgun

1. Introduction and objectives

The oceans, from shallow to the deep waters, encompass a wide range of habitats and environmental conditions which host a huge fauna and flora biodiversity. The unique characteristics of several marine systems have driven a variety of biological adaptations, leading to the production of a large spectrum of bioactive molecules resulting in a living library of diversity which is largely unexplored and underexploited.(1,2)

Modern lifestyles have developed new focus on appearance and personal care which keeps attracting a high number of consumers towards materials used to enhance or alter the function and appearance of the skin, hair and nails. (3) As the market of cosmetics is highly dynamic and new

products are being constantly launched in an extremely fast rate, new concepts have been continuously emerging and new terms have been coined. An example is the term “cosmeceuticals”, which derives from a combination of the words “cosmetics” and “pharmaceuticals”, and refers to cosmetic products with drug-like benefits. Although the Federal Food, Drug and Cosmetic Act does not recognize this term, it is widely used in the cosmetic industry. (4,5)

The word cosmeceutical describes a class of products with bioactive ingredients such as vitamins, minerals, phytochemicals, enzymes, which exist in various types of formulations such as creams, lotions, and ointments. The term implies to the consumer a product purchased without prescription that exert a pharmaceutical therapeutic benefit but not necessarily a biological therapeutic one. (6,7) It is estimated that on average a woman spends 15 000 U.S. dollars on beauty products in her lifetime making the cosmeceutical industries a fascinating, profitable, and constantly growing in the world economy.(3,4,7)

In turn, the most recent concept, representing the latest trend in the beauty industry is “nutricosmetics”, which emerged from a combination of the terms “cosmeceuticals” and “nutraceuticals”. Nutricosmetics are characterized as natural health products with a capacity to improve the function and appearance of the skin, hair, and nails, when ingested. It is believed that these compounds exert their beautification effects within the body. Thus, nutricosmetics are becoming an important trend, since consumers have a growing awareness of the benefits of consuming foods and food supplements, tending to acquire preferentially products from natural origin that can restore and improve health and beauty without posing any prejudicial effects. (4)

Currently, many synthetic chemicals are used in the cosmetic products, but many of them do not match the consumers expectations due to their high cost and negative side effects. Thus, in recent years, the demand for cosmetic products containing natural ingredients is rapidly expanding. They are promoted as green and sustainable materials. The advantages of natural ingredients are environmentally friendliness, fewer side effects, and safer use. Hence, an entire new paradigm of beauty care, combining cosmetics and pharmaceuticals properties into novel products with biologically active ingredients, will be the hallmark of the next decades. (3,7)

Although plant-derived ingredients are still very popular and widely used in cosmetic products, they also have some limitations because plants generally exhibit a slow grow and environmental and culture practices require more investment. On the contrary, marine species not only produce chemically unique biomolecules not found in terrestrial resources but also can be grown rapidly in large quantities and cost effective by modern aquaculture techniques. (4)

From this perspective, the marine environment provides numerous marine organisms with potential bioactive compounds. (3)

2. Methodology for research

The revision was based on several resources from numerous websites like Cosmetics Europe, scientific articles databases like NCBI, Booksc.xyz, ScienceDirect, Crossref, Google

Scholar, Wiley online Library, Dermatologic Clinics and finally, governmental websites such as the European Commission website. All are of public domain.

The scientific information resources, papers and patents date between the year of 2006 and 2021. The key words used to discover the scientific information displayed in the dissertation were: "natural marine cosmetic products", "hydration cosmetics marine", "marine products mass market risks", "ecological cosmetics packaging", "zero waste packaging", "cosmetics regulation in Europe" "innovative ingredients" and "innovation concept marine cosmeceuticals". The information research and analysis process took place between January 2021 and June 2021.

3. Biological Targets and Mechanisms of action of Cosmetic Products

Presently, there is a high demand for cosmetics that function as skin depigmentators, ultraviolet (UV) filters, anti-inflammatory, anti-wrinkle, anti-aging, skin hydrating, antiacne, as well as antioxidant agents. (4)

3.1 Antimelanogenic Activity

Skin whitening refers to the use of natural or synthetic substances that provide an even pigmentation by reducing the melanin concentration in the skin. (1)

Melanin plays an important role in UV-induced photodamage of the skin. It is also the key pigment that contributes to the colour of skin, eyes, and hair in humans.(8) The overproduction or a lack of melanin pigment is simultaneously an aesthetic and biological problem. Minor changes in the physiological status of the human body or exposure to harmful external factors can affect pigmentation patterns either in transitory (such as in pregnancy) or permanent (*e.g.*, age spots) manners. For this reason, there is also a great demand for whitening cosmetics for the treatment of lentigo, pregnancy mask, or even hyperpigmentation in the form of freckles, the so-called "age spots" and melanoma.(4)

A pharmacological tool to control skin pigmentation has been a goal in both the medical and cosmetic areas and has significant implications for skin cancer prevention, photoaging, and aesthetics. (7) The global skin lightening market value is forecasted to reach 8.9 billion U.S. dollars by 2027.(9)

Melanogenesis

Melanin is produced by sequential enzymatic processes in melanosomes, a membranebound organelle residing in melanocytes, and then transferred to surrounding keratinocytes in order to induce homogenous pigmentation and photoprotection. (10) Melanogenesis is regulated by maturation and translocation of tyrosinase. (3) Tyrosinase is a multifunctional, membrane glycosylated and copper-containing oxidase enzyme that intervenes in the early stages of

melanogenesis by the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and subsequently oxidizes DOPA to dopaquinone. (4) The translocation of tyrosinases is regulated by the presence of specific carbohydrate moieties. (3)

Depigmentation

The depigmentation process can be achieved by several mechanisms, such as the inhibition of microphthalmia-associated transcription factor, downregulation of melanocortin 1 receptor activity, interference with melanosome maturation and transfer, melanocyte loss, and inhibition of the tyrosinase enzyme. Since tyrosinase is the rate-limiting enzyme, the inhibition of this biological target is currently the most common approach for the development of skin whitening agents for cosmetic purposes.(4) Until now, the use of synthetic tyrosinase inhibitors (*e.g.,* hydroquinone) is rather limited owing to their toxicity, low stability, poor skin penetration, and low activity. Instead, cosmetics are incorporating natural ingredients, such as liquiritin, isoliquertin, aloesin, arbutin, and vitamin C, as these have less side effects and are more earth friendly. (11,12)

3.2 Anti-aging Activity

Anti-aging products are amongst the most marketed worldwide since ageing signs increasingly become an issue due to the ever-increasing life expectancy. (1,13)

The term “skin aging” refers to the degradation of the extracellular matrix in both the epidermal and dermal layers, manifesting itself by thinning, dryness, laxity, fragility, enlarged pores, fine lines and wrinkles, vasculature prominences, increase in transparency, and loss of elasticity and texture. (4,5)

Intrinsic aging is generally determined by genetic factors; however, extrinsic factors such as exposure of the skin to UV rays, pollution or nicotine, repetitive muscle movements such as squinting or frowning, and lifestyle such as diet, sleeping position, and overall health also contribute to the aging process. Aging is also influenced by a decrease in collagen gene expression, low fibroblast activity, and fibroblast regeneration as well as shrinking of the lamellar barrier, which results in the inability of the skin to retain moisture. Although the mechanisms underlying skin aging are not completely elucidated, the cosmetic industry continues to offer an enormous variety of antiaging products, most of which is claimed to stimulate collagen and glycosaminoglycan (GAG) synthesis by fibroblasts in the epidermis, thus increasing the firmness and flexibility of the corneal layer of the skin. (4)

Antiphotoaging Activity

There is evidence that prolonged human exposure to UVA (320–400 nm) and UVB (280–320 nm) radiation may result in acute and/or chronic effects on the skin and on overall human health as seen in Figure 1. Growing awareness of the risks associated with skin exposure to UV radiation over recent decades has led to increased production and use of solar products worldwide. (1,14)

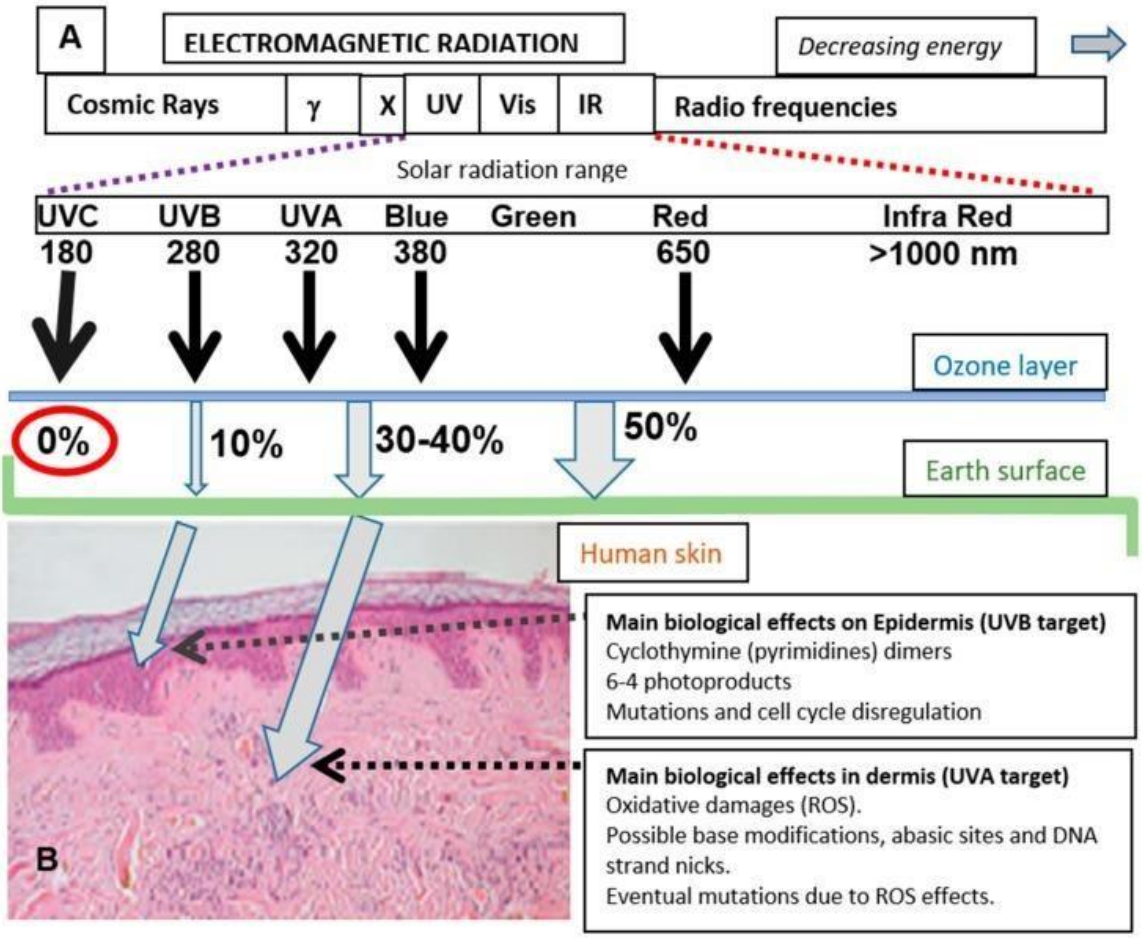

Figure 1- Solar radiation reaching Earth's surface, skin penetrance, and biological effects. (A) Approximate percentage (%) of the total solar radiation reaching Earth's surface for different wavelength regions. (B) Skin penetrance of UVB and UVA. Note that the less energetic UVA radiation has deeper penetrance than UVB. The main cellular consequences are also mentioned. From (74).

The mechanism that causes the majority of the skin deterioration is reactive oxygen species (ROS), generated by inflammatory reactions and by solar irradiation. (5) In extrinsic aging, ROS triggers the various growth factors and cytokine receptors which further stimulate mitogenactivated protein kinase (MAPK) signal transduction and PI3/AKT pathway. The AKT pathway suppresses the expression of antioxidant enzymes in the cell. MAPK upregulates activator protein1 (AP-1) and nuclear factor-κB (NF-κB) in the nucleus. The induction of AP-1 gives rise to the matrix metalloproteinases (MMP) expressions. (3,15) MMPs are a collection of zinc-containing extracellular proteinases that degrade the extracellular components, such as collagen and elastic fibers, inducing wrinkle formation. ROS also activates the expression of the hyaluronidase enzyme

that degrades hyaluronic acid. (3) Hyaluronic acid is present in extracellular matrix, absorbing and retaining water molecules and helping to keep the skin smooth, moist, and lubricated.(16)

Anti-Wrinkle Activity

Inhibitors of MMPs may have potential uses as anti-wrinkle cosmetic products. (17) The MMPs can be sub-divided in three major functional groups, *i.e.*, interstitial collagenases (which degrade types I, II, and III collagen), stromelysins (which degrade laminin, fibronectin, and proteoglycans), and gelatinases (which degrade type IV and V collagens). MMPs expression is usually induced by various extracellular stimuli such as growth factors, cytokines, and UV radiation. Moreover, MMPs overexpression is associated with tissue remodelling, repair, and destruction phenomena. Accordingly, MMPs are useful markers for skin aging and agents that stimulate collagen synthesis. Interestingly, several studies have revealed that nutrient-derived compounds such as oligosaccharides, flavonoids, polyphenols, and fatty acids are able to inhibit the activation and expression of MMPs. Therefore, these compounds could have a strong potential for the development of nutricosmetic products. (4)

3.3 Antioxidant Activity

Oxidative stress is an imbalance between oxidants and antioxidants, and it is mainly caused by ROS and could lead to cellular damage. (8)

Antioxidants encompasses a broad range of molecules with several activities, including photoprotection, and scavenging/immobilizing of ROS such as superoxide anion (O_2^{-}), hydroxyl radical ($HO^{\cdot}$), and hydrogen peroxide (H_2O_2), thus preventing damages of the membrane lipids, proteins, and DNA. (13) They elicit their benefits by preventing, delaying or neutralizing the effects of oxidative change and suppression and/or scavenging of free radicals. (18)

The ability to regulate ROS decreases with age, whereas the production of mitochondrial ROS increases, and therefore, tissues are more susceptible to oxidative stress with age. Since the oxidation of membrane lipids is one of the most important factors that decreases the youthful appearance of the skin, the prevention of ROS formation is fundamental. (4,13)

The consumption of antioxidant-rich food supplements is an important strategy used in the so-called “antioxidant therapy” to maintain health as well as to prevent many diseases such as cancer, cardiovascular disease, and brain dysfunction. (19) Antioxidants consist of enzymatic and non-enzymatic molecules. Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH), glutathione reductase (GR), and glutathione transferase (GST), which are present in human plasma and erythrocytes. Non-enzymatic antioxidants consist of many classes of small molecules such as β-carotene, *R*-tocopherol (TOH), ascorbic acid, and ubiquinol, among others. (4)

The use of synthetic antioxidants (*e.g.*, as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), *tert*-butylhydroquinone (TBHQ), and propyl gallate) for food supplements or medicine has been restricted, due to their lack of safety. On the contrary, natural antioxidants

are considered safer alternatives, and many research efforts have been carried out to discover effective natural antioxidants for the cosmetics industry. (4,20)

3.4 Antiacne Activity

The pathogenesis of acne vulgaris is complex and multifactorial nonetheless, generally, it is viewed as an inflammatory disease with increased sebum production, retention hyperkeratosis and carrying commensal skin microbiota. (21–23)

Propionibacterium acnes and *Staphylococcus epidermidis* are the main bacteria species present in that anti-inflammatory process. These bacteria trigger the production of proinflammatory cytokines and induce the release of ROS whose excessive production results in a destructive phenomenon leading to scarring. They also release lipases to digest a surplus of the skin oil and sebum, which in turn stimulates an intense local inflammation that bursts from the hair follicles. Therefore, the inhibition of both bacteria has been recognized as a strategic method for the treatment of acne in the cosmetics industry. (4,20,22,24)

Acne vulgaris due to the growth of bacteria is traditionally treated with antibiotic therapies such as clindamycin and erythromycin. In some cases, it requires oral antibiotic therapy. However, extensive application of antibiotics has led to bacterial resistance. Besides, antibiotics may cause skin allergies and skin irritation. (21)

3.5 Wound Healing and Anti-Inflammatory Activities

Inflammatory skin diseases are very common dermatological problems that exist in a variety of forms, *i.e.*, from occasional rashes to more chronic conditions such as atopic dermatitis, rosacea, seborrheic dermatitis, and psoriasis. Cutaneous inflammation has been linked to many diseases as well as visible anticipated skin aging. (4)

Wound healing and skin regeneration is a complex and tightly regulated process of recovering the forms and anatomical functions of injured tissues, which consists of three overlapping phases (inflammatory, proliferative and remodelling). The inflammatory response starts with the identification of an inflammatory or infectious origin signal and the release of chemicals from migrating cells and tissues called mediators. Anti-inflammatory drugs achieve their therapeutic effects by receptor activation and enzyme inhibition. Among anti-inflammatory and analgesic drugs, alkaloids continue to be promising therapeutic agents for chronic and severe pain. Anti-inflammatory drugs function by antagonizing the main inflammation enzyme called cyclooxygenase (COX). (4,25)

Repeated trauma, inadequate perfusion or oxygenation and excessive inflammation are factors that contribute to causing and perpetuating the chronicity of wounds. Imbalance has been observed in free radical generations and antioxidants to cause tissue damage and oxidative stress,

and belated wound healing. Elimination of ROS could therefore be a significant strategy for the treatment of chronic wounds. (26)

The most conventional treatments for dermal wounds aim to reduce inflammation (*e.g.*, nonsteroidal anti-inflammatory drugs (NSAIDs), immunomodulatory drugs and topical corticosteroids). These treatments, however, can have a negative impact on wound healing. Although it is pivotal to search for new anti-inflammatory candidates with less adverse effects, the endeavor is quite challenging due to the complexity of the inflammatory process and its role in the host defense. However, recent progress to unravel the mechanisms involved in inflammation has allowed the identification of new targets. (4) Natural products are alternatives to the used drugs which offer hope to discover bioactive lead compounds that may be developed into drugs for treatment of inflammatory disorders. (27) Some examples of natural substances used are β-glucans, honey, aloe, cocoa and oak bark, among others. (28)

3.6 Skin Hydration

Maintenance of the hydration rate is essential to preserve skin integrity. (17) Dry skin may be caused by an imbalance or reduction in the natural moisturizing factor (NMF) of the stratum corneum (SC), and a disruption to the usual process of desquamation, which is also a symptom of ageing. The NMF is mainly comprised of amino acids, which act to maintain cutaneous hydration, thus allowing for normal desquamation and healthy skin. Common treatments of dry skin are topical moisturizers, which contain ingredients to mimic those comprising the natural moisturizing, or are formulated to encourage the occlusion or attraction of water into the epidermis. (13)

The topical application of lipids is common strategy as these compounds can retain water by the process of occlusion, whereas humectants such as collagen and its derivatives act differently by attracting water into the epidermis. Collagen and collagen hydrolysate are common moisturizing active ingredients with little supporting scientific evidence of their hydrating benefits. (1,13,17)

Skin dryness is caused by a loss of the glycosaminoglycan (GAG) hyaluronic acid (HA), a major constituent of the dermal skin matrix found in every tissue and body fluid. HA is responsible for water retention, tissue regeneration and protection from UV radiation. As the body ages HA epidermal content decreases, which slows down moisture replenishment and tissue repair. This reduction also causes loss of skin elasticity, due to the decline in integral linkages between collagen and elastin that are facilitated by HA. As a result, there has been an increase in moisturizers containing HA, yet only a few studies support their action of reducing wrinkles and maintaining skin moisture in topical treatment; therefore, there is a growing interest in discovering replacement molecules. (13)

3.7 Anti-Cellulite and Slimming Care

Cellulite (gynoid lipodystrophy), often called ‘orange peel effect’, is a typical women’s ailment, which mainly appears on the thighs and buttocks. (29) Although cellulite is not a disease, it is a fundamentally a cosmetic issue, especially for post-adolescent women. (30) Cellulite causes alterations in the adipose tissue of the hypodermis region, such as enhanced lipogenesis, decreased lipolysis, and lipid storage within the adipocytes. (31)

Many different hormones are involved in the lipolysis process. Adrenaline, noradrenaline, glucagon and adrenocorticotropin activate the lipases, while insulin inhibits the activity of these enzymes and stimulates the collection of fat in adipose tissue. (29)

Cosmetic preparations containing alkaloids and polyphenols are used to maintain a slim figure, reduce cellulite and remove toxic products from the body. (29)

4. Natural Products

Natural products (NP) are produced by biological sources such as plants, animals and microorganisms, but which occurrence may be limited to a particular taxonomic family, genus, species or even organism. (7) This term is also usually reserved for secondary metabolites because, predominantly, they are not biosynthesized by the general metabolic pathways and have no primary function directly involved in the normal growth, development or reproduction of an organism. (32) These compounds present several advantages when compared with non-natural compounds such as higher chemical diversity with a great potential of having new therapeutic agents availability, biochemical specificity, binding efficiency and propensity to interact with biological targets, which make them favourable lead structures. (7)

The research for novel compounds is constant, mainly due to two reasons: the first one based on marketing criteria, and the second one, the need of replacing molecules that have been banned or have become distrusted by consumers.(31,33)

4.1 Natural vs Organic

Organic and natural are terms often used when describing food, beauty or home care products that can be very deceptive. (34) And we easily understand that skincare brands invest a lot of money in their marketing to make sure they blur the difference between these two terms as much as legally possible.(35)

As far as definitions for natural and organic cosmetics, there is not, at the present time, a European harmonized standard set criteria. There are, however, guidelines as ISO 16128 that offer a framework to determine the natural, natural origin, organic and organic origin content of products based on the ingredient characterization. (36)

The term ‘organic’ refers to how an ingredient is farmed, *i.e.*, it must be prepared and grown without pesticides, chemical fertilizers, genetically modified organisms (GMOs), sulphates/parabens or antibiotics. However, just because the product is labelled ‘organic’ it does not mean it is 100% organic. (34)

A ‘natural’ product can be defined as any material that is derived from a plant, mineral or animal by-product, and which subsequently may have been processed, without chemical reaction, to yield a chemical or chemicals that are identifiable in the original source material. Brands can use this term on their product labels as a tactic because there is no governing body that has laid down the guidelines to specify a product as ‘natural’. (34,37)

Certifications exist to help the consumer make informed decisions on the products they buy, some examples are ECOCERT (figure 2), NaTrue, BDIH, USDA, ORGANIC, COSMOS, Nature & Progrès, etc. Certification bodies follow standards, which can be national standards or their own rules. Most certified products will display their certification labels on the front or back of their packaging. (35,36,38–40)

Figure 2 - ECOCERT Certifications. From (38).

4.2 Innovation Concept

The global market for cosmetic and cosmeceutical products is forecasted to grow at a rate of 4.3% by 2022 with a value of 430 billion U.S. dollars. In addition, consumers’ demand is turning

to natural products due to health concerns and popular trends, forcing research to discover new compounds from the abundant and alternative source represented by marine organisms. (1)

Bioactive compounds produced by marine organisms are still largely unexplored and unexploited. Therefore, the identification of marine derived molecules for (bio)technological and industrial purposes has untapped potential for new discoveries to be included in the composition of personal care products. (1)

4.3 Marine Environment as an Unexploited Source for Innovative Cosmetic Ingredients

Cosmetics are defined as "any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odors". (36)

Cosmetics products with biologically active ingredients purporting to have medical benefits are formulated not only to improve the skin appearance but also to increase positive physiological effects at the cellular level. Simultaneously, it is necessary to discover new bioactive substances with more resourceful, safe and stable properties from natural sources for cosmetic development. (41)

In the most traditional process for bioactive discovery, a natural product is firstly extracted from the source, screened against a specific target, isolated by a bioassay-guided isolation procedure, fractionated and purified, yielding essentially a single biological active compound. Despite its widespread use, this traditional method is slow, labour intensive, barely efficient and provides no guarantee of success. Nowadays, natural products discovery (table 1) is on high demand for rapid screening, hit identification and hit-to-lead faster development processes, being mandatory to explore new, efficient and innovative approaches. (7,42,43)

Table 1– Methods to discover and characterize new bioactive compounds from marine sources (7,42,44–47)

Analytical and spectroscopic methods	High resolution nuclear magnetic resonance (NMR) Mass spectrometry (MS) Thin layer chromatography (TLC)

Metagenomics	Whole genome shotgun sequencing (WGS) Targeted metagenomics Sequence-based approach Function-based analysis
Genome mining	Process of searching the genome for DNA sequences encoding the biosynthesis of novel compounds. Bioinformatics tools, including BAGEL, ClustScan, CLUSEA, NPsearcher, PRISM, and antiSMASH
Gene cluster	Set of genes encoding the same or similar products. For example, a biosynthetic gene cluster will encode for a set of biosynthetic enzymes that undergo linked enzymatic reactions to produce a biochemical compound.
Total chemical synthesis	Despite the characteristic structural complexity associated with marine natural products, there is a remarkable development in their total chemical synthesis, which is often reported shortly after their discovery.

Noteworthy, often the application of several of instrumental methods is needed for unequivocal structural identification of a given compound.(32)

The methods for the detection of the biological activity of extracts, fractions, and pure compounds can best be divided into two groups for screening purposes: general screening bioassays (*e. g.,* Hippocratic screening and Brine Shrimp Lethality Test) and specialized screening bioassays (*e. g.*, DPPH scavenging assay and DPPH - TLC assay). (48) Specific test methods are often cumbersome and expensive. Thus, first the procedure is narrowing the search, once detected the valuable areas, then a battery of specific and more sophisticated bioassays can be employed. (32)

Regarding extraction methods of metabolites from natural matrixes can be categorized into conventional and novel techniques. Conventional methods comprise saponification, maceration, Soxhlet's extraction, classical solvent extraction; whereas newly emerging extraction methods include enzyme-assisted extraction (EAE) microwave-assisted extraction (MAE), pressurized fluid/liquid extraction (PLE), supercritical fluid extraction (SFE), and ultrasound-assisted extraction (UAE). The novel techniques application is preferred as it offers several advantages including lower extraction time, minimum usage of solvents, higher extraction yields, and quality.(49–52)

4.4. Cosmetics from Marine Origin

Marine organisms have evolved biochemical and physiological mechanisms that include the production of bioactive compounds necessary for reproduction, communication, and protection

against predation, infection, and competition. (4) Not surprisingly, many of these compounds have a great potential to improve human health and well-being. (43)

Marine natural products are categorized according to their chemical structures into several chemical classes including mycosporine-like amino acids, polysaccharides, carotenoids, polyphenolic compounds, fatty-acids, peptides, terpenes and alkaloids (table 2). (42)

Bioactive Molecules from Marine Organisms

Mycosporine-like amino acids (MAAs)

MAAs are protective secondary metabolites commonly produced by marine organisms under high UV stress, including cyanobacteria, phytoplankton, lichens, gorgonians, cnidarians, sponges, shrimp, sea urchins, starfish, clams, ascidians, and marine algae. These compounds absorb UVR of 310-360 nm, turning them the most efficient UVA-absorbing compounds in nature, and avoid the production of ROS by dissipating the absorbed energy as heat. The type and accumulation of MAAs in marine algae varied based on season, climate, depth, and environmental variables (i.e., salinity, temperature, and nutrient availability). Unlike photosynthetic pigments, MAAs were invoked to function as passive shielding substances by dissipating the absorbed radiation energy in the form of harmless heat without generating photochemical reactions. (13,53)

Daniel et al. (2004) reported that cream with 0.005% MAAs containing porphyra-334 can neutralize photodamage of UVA as efficiently as a cream with 1% synthetic UVA filters and 4% UVB filters. Hence, MAAs derived from marine algae (*e.g.*, *Acanthophora spicifera and Asparagopsis armata*) can be recommended as photoprotective and anti-ageing materials for skin care products. (53,54)

Chemically, mycosporines are small and water-soluble molecules composed of either an aminocyclohexenone or an aminocycloheximine ring, carrying nitrogen or imino alcohol substituents. When substituted with amino acid residues, they are designated MAAs. (55) MAAs are favored to mycosporines as photo-protective due to not only protecting the skin against UV radiation but also exhibiting a high antioxidant activity, scavenging superoxide anions and inhibiting lipid peroxidation. (1) The potential for cosmetics of mycosporines and MAAs, especially extracted from microalgae, is well known and proved by several patents. However, only very few UV-screening and anti-aging products containing mycosporines and MAAs are commercially available. To our knowledge no cosmetic containing such compounds from fungi and bacteria has been developed so far. (1,13)

Polysaccharides

Polysaccharides derived from the Phyla Crustacea, Phaeophyta and Rhodophyta, exhibit several desirable cosmetic properties, such as water retention, anti-inflammatory, reduced or nil toxicity and broad antimicrobial action. (1) The most well-known polysaccharides with industrial applications are the sulfated (fucoindans, carragenans, laminarans, galactans and ulvan) and nonsulfated (*e.g.*, alginates and agars) polysaccharides extracted from *Kappaphycus*, *Gigartina*, *Chondrus* and many other species. (21,51,56) Some less abundant and currently without industrial

applications are still under investigation such as laminarin, xylans, porphyrans, argassan, and floridean. (56) Marine algae are considered as the most important source of polysaccharides, and chemical structures of these polymers differ according to class and species of algae. (53)

Most of the naturally occurring polysaccharides are neutral or acidic in nature, whereas Chitin and Chitosan are examples of highly basic polysaccharides. Chitin is the second most important polymer in the world following cellulose and it can be transformed into chitosan by a deacetylation process. (57)

So due to the polysaccharides' protective effects on the skin, the development of cosmetic formulations with these ingredients could improve the efficacy, stability and sensorial properties of the formulations. Data from clinical studies show that the polysaccharide-based formulations promote transepidermal water loss reduction, protecting the skin barrier function and maintenance of its structure integrality. (58)

Carotenoids

Carotenoids are natural pigments found in all photosynthetic organisms and some nonphotosynthetic archaea, bacteria, fungi, and animals. These photosynthetic pigments consist of two classes of molecules: carotenes and xanthophylls. Carotenoids play an important role in photosynthetic light-harvesting complexes; they absorb the solar spectrum in the blue-green region and transfer the energy to chlorophylls. Furthermore, carotenoids also act as a photoprotectors in photosynthetic organisms. (53)

As photosynthetic organisms, algae can synthesize three types of pigments, which determines their color: chlorophylls, carotenoids and phycobiliproteins. The green color is caused by the presence of chlorophylls a and b. The red color is attributed to phycobilins, such as phycoerythrin and phycocyanin. The pigments in brown algae are usually chlorophylls a, c1, and c2 b -carotene, and fucoxanthin. (21)

Despite data suggesting that several marine carotenoids are efficient antioxidants, few are present in topical cosmetics or sunscreens, due to a lack of promising data from *in vivo* trials. Oral supplements containing marine antioxidants to improve skin health have scarcely reached the cosmetic market due to their low bioavailability. The absorption efficiency and biocompatibility of marine carotenoids on the skin are yet to be determined and will be crucial in understanding their true potential as antioxidant sunscreen ingredients. (13)

Polyphenolic compounds

Polyphenolic compounds are secondary metabolites with diverse biological functions such as photosynthesis, reproduction, cell division, antioxidant and anti-melanogenesis activity. (21,53) The three main groups of polyphenols are phenolic acids, flavonoids, and tannins. Marine algae-derived polyphenols have been investigated for their photoprotective activities. Dieckol, phloroglucinol, fucofuroeckol-A, and triphlorethol-A are some examples that exhibited prominent protective effect against photodamage induced by UVB radiation. Findings confirm the

effectiveness of phloroglucinol as potential cosmetic leads for the formulations of sun-protective lotions and creams. (53)

Fatty acids (FA)

FA are known dietary supplements that also have a broad spectrum of topical applications in cosmetics. Their role includes soft tissue repair and skin nourishment through stimulation of collagen production as well as anti-inflammatory and wound healing properties. Among the different FA, polyunsaturated fatty acids (PUFA), and specifically the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been linked to several health benefits such as healthy aging. (1,59)

The main source of omega-3 fatty acids for human consumption is fish. However, due to its shortage and the consequent increase in price, to satisfy current demand of DHA and EPA research has started to focus on alternatives to fish oil such as oil from plants, algae, bacteria and fungi. The term "single-cell oils" (SCOs) refers to oils produced by single-cell microorganisms such as yeasts and molds. SCOs produced by microorganisms offer many advantages compared to fish oil, including the higher growth rate and oil content and the presence of a number of natural antioxidants such as carotenoids that prevent omega-3 fatty acids oxidation. (1)

Omega-3 fish oils (FOs) are dietary FA transported to the stratum corneum and are able to improve cutaneous health through oral administration. The potential of FOs in topical moisturizers was not assessed in this research. (13)

Similarly, the oil of the deep-sea perch, *Hoplostethus atlanticus*, exhibit moisturizing and emollient abilities comparable to that of petroleum-based products like Vaseline®. The oil produced is a wax reported to improve skin dryness up to 70% as efficiently as petrolatum products. However, *H. atlanticus* is reported as vulnerable to exploitation due to its late maturity, slow growth and low fecundity, therefore has not been considered as a sustainable source for skin moisturizing products, despite its significant moisturizing capacity. (13)

Similarly, the oil of squid, *Loligo loligo*, is a new source of omega-3 and omega-6 oils, where 13% of the wet weight of an adult squid equates to oil, with a high percentage of linoleic acid, EPA and DHA. The aquaculture of squids is yet to be explored; however, *Octopus vulgaris* aquaculture is currently being developed and has shown some early success. Cephalopods are considered good candidates for successful aquaculture, due to their short life spans, early maturity and easy adaptation; therefore, this route of production of omega-3 and omega-6 oils merits further investigation. (13)

Proteins and Peptides

Collagen is the major structural protein of connective in both invertebrate and vertebrate organisms. (60) Many cosmetic formulations have collagen as a major component because of its

significant benefits as a natural humectant, moisturizer, anti-aging, anti-wrinkling and excellent repair and regenerative component to the skin. (60,61)

Proteins of higher molecular weight, such as collagen, cannot be absorbed by the stratum corneum of the skin; instead, they remain on the surface working as water-uptake through hydration and as protectors against microbial infiltration in cases of wounded tissue. (61,62)

Marine collagens should be a true alternative since bovine collagen sources are scrutinized due to regulamentary concerns. Sea collagen can be derived from several marine fish, as well as organisms belonging to the phyla Porifera, Echinodermata, Cnidaria and Mollusca. Some marine collagen has even shown better biocompatibility than collagen obtained from other animal sources and improved mechanical strength, however, has a lower degradation temperature and therefore more limited application. (13,17,60,62)

Future research directions on collagen application for cosmetic purposes may be focused on increasing the denaturation temperature of several types of collagens extracted from fish species. Such an increase of denaturation temperature may expand collagen application. (63)

Alkaloids

Alkaloids were categorized into seven subclasses including pyridoacridine, indole, pyrrolizidine, isoquinoline, guanidine, amino imidazole, and steroidal alkaloids.(42) Alkaloids have been obtained from different marine organisms like sponges, tunicates, anemones, algae and molluscs. From the biological activity point of view, alkaloids show several bioactivities including antioxidant and anti-inflammatory activity. (7,42,64) Potential applications include sunscreen and anti-cancerous drugs. (65)

Studies suggest that a twice daily application of a topical facial cream containing an alkaloid improves the appearance of the skin in patients with mild to moderate rosacea. As rated by the physician, skin appearance improved in 70% of the patients, and 50% of the patients self-reported an improvement following 30 days of topical application. (66)

Terpenoids

Terpenes and terpenoids, which are a modified class of terpenes, are aromatic hydrocarbon molecules found in most plants. They create the scents and flavours, so instead of relying on artificial scents that may be potentially harmful these should be used. They also show a broad range of biological activities, such as antioxidant and anti-acne. (67–69)

Clindamycin is generally used for curing acne as a clinical treatment. However, Clindamycin was shown to be bacteriostatic even at 4 × MIC, whereas Sargafuran, a terpene, showed bactericidal activity against P. acnes, minimizing the chance of development of resistance. (22)

Studies in vitro of the cutaneous penetration of terpenes applied in pure essential oils or in dermatological formulations (o/w emulsion, oily solution or hydrogel) containing 0.75 % w/w of the essential oils were made. Different skin absorption was observed depending on the type of the

vehicle and terpenes. Cutaneous accumulation of terpenes were several times higher when applied in pure essential oils rather than in topical vehicles. (70)

Table 2 - The marine molecules, their sources, actions, applications and limitations.

Molecule Class	Bioactive molecules	Sources	Actions	Limitations and Applications	Ref.
MAA	Mycosporineglycine:valine	*Palythoa tuberculosa, Porphyra tenera, Lissoclinum patella*	Antioxidant effects: lipid peroxidation and radical scavenging.	High reactivity, instability preventing them from reaching the market	(13) (21) (71) (72)
	Porphyra-334, shionine, Palythine	*Porphyra umbilicalis*	Antioxidant: Photoprotection and anti-aging.	N/A Cosmetic formulations have reached the cosmetics market under the trade names Helionori® and Helioguard 365®	
	Porphyran	*Porphyra tenera, Porphyra yezoensis P. haitanensis*	Antioxidant and immuno-modulating.	N/A Skin whitening products	

	13-O-(b-galactosyl)porphyra-334	Cyanobacteria *Nostoc sphaericum*, microalgae**,** macroalgae *P. umbilicalis* (red algae), yeasts, fungi, sponges, corals, and animals	Antioxidant: radical scavenging, UV protective (absorb UVA radiation). Reduces the damage caused by ROS and thus can prevent skin inflammation and DNA damage.	N/A Explored to develop novel UV filters for sunscreen products to prevent the photodamage. Can be considered as an alternative aimed at reducing the amount of synthetic filters in sunscreen formulations. Moreover, the combination of vitamins A, E, C and G. biloba with red algae extracts can	
				significantly improve the performance of the sunscreens.	

Carotenoids	Astaxanthin (ASX)	*Agrobacterium auranitiacum*, *Pneuoatophorus japonicas*, *Oncorhynchus mykiss*, *Sehola quinqueradiata*,, *Undaria pinnatifida*, *Euphausia superba* and *Haematococcus pluvialisis*	Is among the strongest pigmented antioxidant produced by many microalgae which is responsible for the red colour often associated with crustaceans such as shrimps, crabs, and lobsters. In fact, increasing evidence suggests that ASX is a stronger antioxidant than vitamins C and E, or than other carotenoids such as β-carotene, lycopene, lutein and zeaxanthin. Kerocarotenoid with depigmentation properties that can reduce melanin production by 40% in skin cells protecting skin from flakes and age spots.	N/A Orally and topically administered ASX has shown significant visual improvements in the appearance of skin wrinkles, elasticity, age spots and increased cutaneous hydration in clinical trials. ASX may have applications in dry skin moisturizers as well as anti-ageing formulas.	(1) (13) (17) (21) (25) (31) (53) (73) (74) (75) (76) (77)
	Zeaxanthin	*Nannochloropsis oculata*, *Agrobacterium auranitiacum*, *Haematococcus pluvialisis*, *Pneuoatophorus japonicas*, *Oncorhynchus mykiss*, *Sehola quinqueradiata*,	Antioxidant: limit retinal oxidative damage by absorbing incoming blue light and/or quenching reactive oxygen species.	N/A	

	Undaria pinnatifida			
Fucoxanthin and two prime metabolites: Fucoxanthinol and amarouciaxanthin A	*Agrobacterium auranitiacum, Haematococcus pluvialisis, Pneuoatophorus japonicas, Oncorhynchus mykiss, Sehola quinqueradiata, Undaria pinnatifida*	Antioxidant Fucoxanthin has been demonstrated to stimulate filaggrin promoter activity in UV-induced sunburn. Filaggrin is a UV-sensitive gene that reflects the state of the skin damage. This stimulation of a UV-sensitive gen promotor by fucoxanthin suggested that other protective mechanisms of fucoxanthin might be exerted by the promotion of skin barrier formation through the induction of UV-sensitive gene expression.	Fucoxanthin does not retreat UV-B-damage or protect skin from UV-B radiation, since its UV-B absorption is quite weak. Photoprotection mechanisms might also be achieved by oral administration. It is widely used as an ingredient in health care products for its immune boosting properties. This suggests that fucoidan may be used as a new anti-pigmentation ingredient in medical and cosmetic fields.	

	Lutein/lutein B, Tunaxanthin, Halocynthiaxanthin, β-carotene, lycopene	*Agrobacterium auranitiacum, Haematococcus pluvialisis, Pneuoatophorus japonicas, Oncorhynchus mykiss, Sehola quinqueradiata, Undaria pinnatifida, Dunaliella salinawhich*	Antioxidant: radical scavenging. Anti-aging properties: Prevention of skin spots formation and whitening agent.	More investigations are required before their use in cosmetic formulations. Oral or cutaneous administration. Some commercialised oral supplements. Despite carotenoids being photo-protective compounds, they are more used for their antioxidant properties in sunscreen formulations.	

	Saproxanthin and Myxol (Two rare carotenoids)	New strains of marine bacteria belonging to the family *Flavobacteriaceae*.	Reinforce biological membranes, decreasing permeability to oxygen and enhancing protection against oxidation. The antioxidant activities of saproxanthin and myxol were even greater than those of the commonly used zeaxanthin and βcarotene.	These new and rare marine carotenoids require a thorough evaluation before their implementation within cosmetic products.	
	Unspecified flavonoids/tannins (e.g.,sulphated flavonoid luteolin 7sulphate)	*Lithrum salicaria, Frankenia pulverulenta, Pistacia lentiscus, F. laevis Phyllospadix iwatensis*	Antioxidant: radical scavenging, metal chelation. Photoprotectants	Potential cytotoxicity	(13) (21) (53) (74)

Polyphenols compounds	Phlorotannins: diphlorethol, triphloroethol, trifuhalol, tetrafuhalol, phloroglucinol, eckol, dieckol, fucofuroeckol-A, and triphlorethol-A and eckstolonol	*Halidrys siliquosa, Ecklonia cava, Ascoseira mirabilis, Cystosphaera jacquinotii, Ishige okamurae Sargassum polycystum, Ecklonia stolonifera, S. silquastrum, Eisenia sp.*	Antioxidant: UV protective, radical scavenging Anti-melanogenesis/skin-whitening effects	Up to a certain concentration did not exert any toxic effect, anticipating its potential use in formulations of sun-protective lotions and creams. Several topical formulations are already available for the management of several skin disease.	
Alkaloids	Scytonemin	Cyanobacteria	Scytonemin is a UVA inducible pigment, able to reduce up to 90% of UV-A radiation into the cells. It also absorbs in the UV-B range.	N/A Generally, common sunscreen products contain organic and/or inorganic filters.	(4) (13) (78) (17) (31) (79) (80)
	Topsentin	*Spongosorites genitrix*	Anti-inflammatory activity in UVBirradiated human epidermal keratinocytes.	N/A	

	Phytohormones (e.g., abscisic acid)	*Pyropia yezoensis* *Bangia fuscopurpurea*	Potential inhibition of skin proteases and ROS.	N/A	
	Benzodiazepine's alkaloids: Circumdatins I, C, G	Marine Fungus of the genus *Exophiala*	UV-A screening activity.	N/A	

Polysaccharides PSs ( )	Carrageenans	Extracted mainly from *Kappaphycus* species and *Eucheuma* genera (cultivated) And less from *Gigartina* and *Chondrus* species, *Halichondria panicea*	Gel-forming, emulsifying, thickening, and stabilizing agent. Antioxidant, antibacterial and immunomodulatory effects. Recently, photoprotective effects have been reported. The addition of carrageenan to a broad spectrum of skin care and cosmetic products might decrease UV-induced photodamage compared with sunscreen alone.	N/A Considered as safe additives, used in composition of cosmetic and skin care products for their antioxidant, tonifying, cleaning, hydrating, and revitalizing bioactivities. SEA MOIST COMPLEX® is a marine agent that combines glycerin, sea water and the alga Kappaphycus alvarezii.	(1) (4) (13) (17) (21) (28) (31) (43) (53) (56) (79) (81) (82)

	Chitosan	Marine crustaceans, mollusks shells, shrimp and crabs	Antibacterial activity, wound healing applications and hydrating agents.	Easily obtained and is a promising material for many applications, including biomedical, pharmaceuticals, cosmetics and cosmeceuticals. Active ingredients in dental, skin, hair and nails care.	(83) (84) (85) (86) (87) (88) (89)

	Sulphated polysaccharide: fucoidan, also called fucan, fucosan or sulfated fucan.	*Fucus vesiculosus Laminaria japonica, Kjellmaniella crassifolia, Fucus vesiculosus, Sargassum binderi, T. conoides, Sargassum hemiphyllum, Nemacystus decipiens, Cladosiphon okamuranus, Undaria pinnatifida, Eisenia spp., Ecklonia spp., Ascophyllum nodosum, Lessonia nigrescens, Sargassum polycystum*	Indirect anti-melanogenesis. Radical scavenging, antioxidant, anti-inflammatory, angiogenesis and UV protection. Clinical potential for dermal wound healing. Fucoidan structures and bioactivities are different among brown algae species. Recently, it was reported that topical applications of low molecular weight fucoidans (LMF) (mostly absorbed before irradiation) have stronger photoprotective activity than high molecular weight fucoidans (HMF).	N/A Considered as safe additives. Myriad of pharmacological effects and its non-toxic edible resources. Active ingredients, photoprotection, skin-whitening and antiaging products (attenuate blemishes, wrinkles and freckles) but has not yet been pursued as a cosmetic ingredient given that the data are preliminary.	
	Laminarin	*Eisenia bicyclis, Laminariaceae family Ascophyllum, Undaria, Fucus genera*	Active ingredients, photoprotection and antiaging products. Wound-healing, immunomodulatory, scavenging, antibacterial and antioxidant activity. Modulatory effects on skin cells, hydro-gelling properties.	N/A	

	Bacterial EPS	*Polaribacter sp.* and *Phyllobacterium sp*	Water absorption and humectant.	No in vivo or in vitro data available	
		Vibrio diabolicus	Stimulated HA synthesis and fibroblast proliferation and skin hydration.	Only patent literature available (US 9,393.260 B2)	
		Unspecified marine bacteria	Anti-aging and moisturising.	N/A Commercialized: Hyanify™ and Hyadisine®.	
	Alginates, also known as algin	*Turbinaria conoides, Macrocystis pyrifera, Sargassum horneri, L. digitata, Ulva compressa* and *E. maxima*	Free radical scavenging activity and gel-forming activity.	Alginates are non-toxic hydrogels with excellent biocompatibility properties, used as emulsifier and thickening agent. Peeling products (Macroalgaebased microparticles exfoliated dead skin cells effectively)	

	Agar Agar-agar, is a general name for agarose and agaropectin	*Gelidium amansii*	Scavenger properties, antioxidant and gel-forming activity.	N/A Thickening agent (brilliant gelforming substance) It has the ability to withstand near boiling-point temperatures, making it ideal for use in jellied preparations since the ingredients can be treated at high temperatures and then cooled.	
	Deepsane	*Alteromonas macleodii* Also produced by microalgae.	Emulsifying, thickening, absorption and gel formation.	N/A Deepsane has been marketed as Abyssine® for soothing and reducing irritation of sensitive skin against chemical, mechanical and UVB aggression.	
	HE 800, an exo-saccharide analogous to hyaluronic acid.	*Vibrio diabolicus*	Emulsifying, thickening, absorption and gel formation and anti-wrinkles. Ability to stimulate collagen structuring, the production of HA and keratinocytes and increasing the moisture content of the skin.	N/A	
	Ulvans	*Ulva* and *Enteromorpha genera*	Gel-forming, skin protective and antioxidant properties.	N/A Skin aging products	

	Xylans and mannans	*Bryopsidales* order	Gel-forming and other biological properties. Emulsifier and thickener.	N/A	
	Exopolysaccharides (EPS)	*Agrobacterium sp.*, *Alcaligenes faecali*, *Xanthomonas campestris*, *Bacillus sp.* *Alteromonas macleodii*, *Pseudoalteromonas* sp., *Vibrio diabolicus*, *Polaribacter* sp. and *Phyllobacterium* sp	Emulsifying, thickening, absorption and gel formation and anti-wrinkles. Formulation of anti-aging products. This mixture, obtained through fermentation, enhances the synthesis of collagen I, contributing to the amelioration of skin structural properties. Significant water-absorbing properties that exceeded those shown by common cosmetic humectants, including HA.	Few examples of marine bacterial EPS have found their way into products, including Hyadisine® and Hyanify™. The scope for discovery of novel extremophile EPS is great, due to their relatively unexplored biochemical diversity. This may offer a promising route to new bioactive molecules with moisturizing or anti-ageing actions.	

Fatty acids	PUFAs DHA	Most marine animals obtain long-chain PUFAs from their diets and few are known to produce these compounds: Marine fungi, bacteria and thraustochytrids (e.g., Schizochytrium, Aurantiochytrium and Ulkenia)	Soft tissue repair, skin nourishment and stimulation of collagen production.	DHA-rich oils from thraustochytrids are currently on the market particularly for applications in nutraceuticals and aquaculture. However, they also have a great potential for cosmetic and cosmeceutical applications. To our knowledge, the use OF PUFAs in cosmetic and cosmeceutical sectors has not been addressed yet. Oxylipins are the oxygenated products derived from PUFAs which exhibit innate immunity in response to environmental stress such as wound, metal toxicity and pathogenic bacteria.	(13) (17) (21) (53) (79)
	Omega-3 and -6 oils, EPA	Several species of marine and freshwater fish, *Loligo loligo* And the genus *Nannochloropsis*	Reduced irritation and TEWL, skin hydration.	Not trialled as topical treatment. Linoleic acid (an omega-6 fatty acid) acts as a precursor for ceramide lipid molecules, which comprise half of the extracellular lipid matrix, an important factor of the SC permeability barrier (SCPB). The SCPB reduces both transepidermal water loss (TEWL) and pathogenic	

				invasion; therefore, loss of lipid components. May cause skin dryness.	
	Fish oil wax ester containing fatty alcohols/acids	*Hoplostethus atlanticus*	Skin hydration	N/A	
Proteins and peptides	Marine collagen	Fish skin/bone, echinoderm tests, cnidarians, cephalopods. *E.g.,* *Nemopilema nomurai* *Chondrosia reniformis*	Wound dressing and scaffolding applications. Moisturizing effect through water absorption and preventing skin dehydration. Moisturising and increased skin lipid content.	Preliminary data, prospective outcomes, insolubility. No significant difference in skin hydration between the sponge collagen treatments and the existing collagen product control. Despite these similarities in the efficacies, it is highlighted as an additional source of collagen.	(13) (61) (90) (91) (92)
	Unspecified serine endo-protease	*Salmo salar*	Skin rejuvenation ingredient: Wrinkle reduction, anti-erythema, pigment correction, skin hydration. It is also shown to be capable of enzymatic exfoliation of dead keratinocytes whilst stimulating new skin cells to grow.	Without any adverse side effects. Commercialised: Zonase enzyme.	

	Tripeptide containing argininegly cine-aspartic acid	*Ulva lactuca*	Anti-aging, wrinkle ameliorating, skin elasticity improving and skin infiltrating effects.	N/A	
Terpenoids	Tetraprenyltoluquinol chromane meroterpenoid (TPM)	*Sargassum muticum*	Photodamage attenuation on irradiated cells with UVA light, presented protection against intracellular ROS generation and compared to retinoic acid TPM has a better performance.	No display of toxicity against human dermal fibroblast cells.	(7) (22) (23) (93)
	Meroterpenoids (structural similarities with αtocopherol)	*Cystoseira* and *Sargassum* sp.	Radical scavenging properties exhibited strong radical scavenging activity, protection against UV-irradiation, inhibition of lipid peroxidation and O2−, antifouling and antiinflammatory properties.	N/A They have been suggested for topical application as an effective strategy to prevent skin ageing, due to their antioxidant properties.	
	Cembrene diterpenoids	The soft coral *S. flexibilis*	Anti-acne skin care products or therapeutic agents Do not directly inhibit bacterial growth but use another pathway to reduce bacteria-induced acne effectively without antibiotic resistance.	Low side effects	

	Sargafuran	*S. macrocarpum*	Anti-acne cosmetics	N/A Stable against heating up to 60 °C, pH 4–7 and irradiation for 24 h. These properties are suitable for cosmetics or skin care products to prevent acne.	
Polyphenols compounds	Unspecified flavonoids and tannins, phlorotannins: phloroglucinol, eckstolonol, eckol, phlorofucofuroeckol, dieckol, 7-phloroeckol, quercetin	*Sargassum polycystum, Ecklonia stolonifera, E. cava, S. silquastrum, Pistacia lentiscus, F. vesiculosus, L. digitata, Furcellaria lumbricalis, Pelvetia wrightii, Gelidium cartilagineum, Pelvetia canaliculate*	Tyrosinase inhibition, anti-melanogenesis Anti-cellulite (Lipolytic agents) Stimulates blood flow and reduce the appearance of cellulite, but not eliminate it. Slimming effects	Generally believed that these compounds are safer. The safety question originated from the idea that the active principles are not isolated, but instead exist in a complex and stable chemical clusters that prevent their negative effects on the site of application. Anticancer therapies. Sunscreens. Anti-skin aging products. Prevention of collagen premature degradation, wrinkle formation and the appearance of cancer cells.	(13) (17) (31) (74)

	Sulphated flavonoid: luteolin7-sulphate	*Phyllospadix iwatensis*	Indirect anti-melanogenesis	N/A	

Natural Products by Taxon

Taxonomic experts have historically performed the identification of sampled organisms yielding new natural products, with voucher specimens being deposited in museums or institutional collections. In the past few decades, the science of taxonomy has been continuously updated, particularly with the advent of molecular genetics. Consequently, taxonomic information has been regularly revised and updated with description of new species. (94)

The selection, for pharmacological purposes, of macro or microorganisms must be grounded on a correct taxonomic identification and classification. An incorrect classification of a species may compromise an entire drug discovery project, not only because it is impossible to reproduce the isolation in the event of a bioactive extract and/or metabolite, but also because it can mislead the dereplication process—the process by which the new bioactives are identified. (43)

Porifera

Sponges are sessile marine invertebrates, attached to the ocean floor, and use highly evolved chemical compounds to attract food, block the growth of intruding species into their habitat or repel predators. Therefore, they have evolved the ability to synthesize toxic compounds or to obtain them from marine microorganisms. (32) Thousands of sponges species have been identified so far and each produces a different set of secondary metabolites to help them occupy their particular niche. Besides being one of the richest sources of interesting chemicals, sponges act as hosts to a variety of symbiotic/parasitic organisms including blue-green algae and bacteria that also produce a vast array of bioactive secondary metabolites. (32)

Sea sponges are a renewable natural resource. They are highly absorbent, softly textured, and suitable for the most delicate skin. Natural sponges are stronger and last longer than the synthetic counterparts because they are more resistant to abrasion and have enzymes in them that prevent the growth of mold, mildew and bacteria. In addition, natural sea sponges are better for bathing and cleaning because they soak up and hold more water without drenching. (41)

The marine sponge comprises a rich reservoir of species and natural products with diverse chemical structures and biological properties (*e.g.*, antimicrobial and inhibitory effects on cancer cell lines*)* with potential application in drug development. (95) The sponge symbiosis is of known importance to the sponge health, survival and metabolite production. (96) By a combination of gene engineering, pathway reconstructing, enzyme engineering and metabolic networks, these microbes can be modified, isolated, and kept in culture to produce more novel chemicals containing enhanced structural features or a large quantity of known valuable compounds for pharmaceutical production. (95)

Chordata

Ascidians (urochordates, tunicates), commonly known as sea-squirts, belong to the Phylum Chordata that consist of three lineages, the urochordates, the cephalochordates, and the vertebrates. (4) There are over 3000 species of ascidians, they exist below low-tide levels in protected areas with good water movement and often form symbiotic relations. Natural products synthesised by

ascidians include alkaloids and peptides. (97) Many can tolerate and accumulate heavy metals and have anti-inflammatory activity. It has been suggested that it may be involved in chemical defence against predators and microbes, or in metabolic roles such as oxidation and reduction reactions. Ascidians are important ecologically due to their invasive potential and adverse effects on native fauna and aquaculture. (98)

Cnidaria

Cnidaria have been relatively under-exploited to obtain natural products compared to other taxa. Most of the natural products extracted from Cnidaria derive from benthic cnidarians, while a limited number of bioactive compounds have been extracted from pelagic cnidarians (hydromedusae and scyphomedusae). Scyphomedusae have been found to possess mainly three categories of compounds with biotechnological applications: collagen, fatty acids and bioactive compounds extracted from the crude venom of their nematocysts (*e.g.,* glycoproteins and phosphoproteins). (4,99)

Scyphomedusae have been considered a nuisance to human populations due to their interference with human activities along the coast. However, the positive effects of a diet that includes, for example scyphomedusae *Rhopilema esculentum*, *Rhizostoma pulmo and aurelia coerulea* are very popular across China and the whole Southeast Asia, as food are being supported by scientific studies that are confirming their nutraceutical value as well as their application in the cosmeceutical, biomedical and biomaterial fields as antioxidants and antiphotoaging agents. (53,100,101)

Echinoderms

Regarding the marine resources in wound healing, none can compare with sea cucumbers. (3,31) Dried or extracted, sea cucumbers are commercially marketed as sea cucumber extracts and are frequently blended to produce medicinal products in the form of nutritional supplement, either in capsules or tablets, ointment, toothpaste, body lotion, and facial cleanser. (102)

Sea cucumbers, especially *Stichopus hermanni*, commonly known as “gamat emas”, contain active ingredients such as proteins, glucosaminoglycans, chondroitin sulphate, cell growth factor and fatty acids, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that are important for wound healing process because they accelerate the wound contraction rate. (85)

When treating a burn wound, the topical application with a *S. hermanii* based hydrogel wound dressing resulted in a significant wound contraction rates at day 21 and 28 post-burn wound. On the contrary, no significant differences were detected at day 7 and 14. This effect might be due to the cross-linked “gamat hydrogel (*S. hermanii*) dressing” that confers it the capacity to retain the active ingredients and delays their delivery on the wounded skin, thus acting at a later stage of the wound-healing phase. The advantage of this hydrogel dressing is that biologically active compounds are immobilized for a longer period in the hydrogel matrices, thus creating a sustained and controlled release system that could significantly enhance the activity of the incorporated sea cucumber extract during tissue repair and effectively interact with the wounds facilitating the healing process at a later stage. (3)

The sea cucumber *Stichopus choronotus* was also found to act at the initial phase of the wound healing process. Since the presence of excessive free radicals is associated with impaired wound healing, the radical scavenging properties of the antioxidants (*e.g.,* phenol and flavonoid) present in the aqueous extracts of cucumbers would contribute to wound healing. EPA and DHA, the major fatty acids in sea cucumbers, also intervene in the process of inflammation by stimulation of the production of resolvins (which primarily inhibit IL-1β production) and protectins (which inhibit TNF-α and IL-1β production) through COX-2 and 5-LOX pathways. (4)

The anti-inflammatory effect of sea cucumbers in clinical settings was also studied by incorporating sea cucumber extracts into Carbopol® gel base and applied topically to diabetic foot ulcer patients for 12 weeks. It was suggested that the saponin content in the extracts of sea cucumbers may play a role in preventing the lipopolysaccharide-induced production of TNF-α by nuclear factor-κB (NF-κB), which is a transcription factor that regulates the transcription of many genes involved in the inflammation process.(10)

Macroalgae

Macroalgae or seaweeds are aquatic, photosynthetic organisms taxonomically categorized as algae, and they are divided into three categories (phyla) based on their pigmentation, the Rhodophyceae (red algae), Phaeophyceae (brown algae), and Chlorophyceae (green algae). (17,103) Macroalgae represent an economic, biodegradable and non-toxic source of natural moisturizers (alginate, agar, carrageenan or fucoidans). (31) In recent years, seaweeds have been one of the most extensively studied marine organisms for their bioactivity (delay skin aging, antioxidant and immunomodulatory activity) and bioactive compounds (polyphenols, fucoidan, phlorotannins, carotenoids, etc). (4,31)

Seaweeds are well-known polysaccharide producers, being commonly applied as hydrocolloids in different industries. Their protein content is highly dependent on the macroalgae type, since brown ones have low amounts (5–15% of the dry weight), whereas green and red can reach values near 50% (10–47% of the dry weight). Among these nutritional values, macroalgae have a high content in micro-nutrients, which includes vitamins (mainly B3, B9, B12, C and E) and antioxidants, such as polyphenols (*e.g.,* phlorotannins) or pigments (carotenoids and chlorophylls). (17)

Rhodophyceae **(red algae)**

Protecting DNA and slowing the devastating effects of free radicals are two of the most common actions in anti-aging cosmetics. *Corallina officinalis* is a heat-resistant organism that forms calcium-rich structures similar to coral, which is an interesting source of cosmetic active ingredients with DNA-protecting properties. In spite of its resemblance to coral, *Corallina officinalis* is classified as a plant and the special porous skeleton that forms tunnels and pores makes it one of the most complex marine structures in the world of algae. Its usefulness in cosmetic science is based on its ability to act as a filter of UV and infrared radiation, which can produce damage to cellular DNA. The filtering capacity of *C. officinalis* is due to the crystallizing of the carbonates it generates in rhombohedrons with magnesium ions. The absorption spectrum of these structures

includes a section of the spectrum that enables it to protect against infrared and UV radiation. Its ability to protect DNA was determined by measuring its ability to repair previously damaged DNA. Its activity as a protector against the aggression caused by oxygen free radicals has also been evaluated. The results obtained showed that it is capable of offering protection both to the DNA, from damage caused by UV radiation, and the lipids in the membrane, from the oxidation caused by free radicals. (104)

***Phaeophyceae* (brown algae)**

Some types of brown macroalgae are used in cosmetics due to the presence of vitamins, minerals, amino acids, sugars, lipids, and other biologically active compounds such as agar, alginates, and carrageenans. For example, *Macrocystis pyrifera* alginates are manly applied as a thickening or gelling agents and emulsion stabilisers in cosmetics. (103)

Polysaccharides (*e.g.,* alginates and fucoidan) isolated from *Ecklonia maxima* possess strong antioxidant properties, anti-melanogenesis actions, and photoprotective activities. Suggesting that *E. maxima* may be an ideal ingredient in the pharmaceutical and cosmetic industries. (8)

***Chlorophyceae* (green algae)**

Green algae (*e. g., Caulerpa racemosa, C. sertularioides, C. serrulata, C. lamourouxii* and many other species of *Chlorophyta*) are an offering source for cosmetic colorants, phenolic compounds, sterols, vitamins and other therapeutic agents such as caulerpin and caulerpic acid. Some of the bioactive agents isolated are used as skin moisturizing and protecting agents, creams with anti-stretch markings, body ointments, eye balms, face masks, antiaging washing gel, natural sunscreen, body scrubs, face peeling and face salves, firming body liniment, body unguents, purgative gels, and many others uses. (25)

Microalgae

Microalgae are microscopic unicellular organisms capable of converting solar energy into chemical energy via photosynthesis. They produce a wide range of bioactive metabolites such as proteins, lipids, carbohydrates, carotenoids and vitamins that can be exploited for commercial use in food or cosmetic industry. Some microalgae species are explored in the cosmetics industry, especially the genus *Arthrospira* and *Chlorella*. Extracts from microalgae are incorporated in many face and skin care products (e.g., anti-aging cream, refreshing or regenerating care products, emollient and anti-irritant in peelers), sun protection and hair care products. (5)

Dermochlorella DG® from CODIF Reserche & Nature, a *Chlorella sp.* extract containing oligopeptides acts as restructuring actives on the dermal-epidermal junction to increase firmness and skin tone. (5)

XCELL-30® from Greensea is developed from microalgae endemic to Madagascar, and specifically acts on cellular turnover in the basal layer of the epidermis, thus allowing the preservation of the youthful characteristics of the skin. (13)

Alguronic Acid® from Algenist, a novel microalgae powerful compound is responsible for regenerating and protecting the microalgae cell in harsh environments and conditions. When scientifically tested, Alguronic Acid® demonstrated significant anti-aging properties, helping to rejuvenate the skin for a more youthful appearance. (17)

Alguard® is a natural sulfated polysaccharide compound isolated from *Porphyridium sp.*, that acts as a shield, creating a thick protective layer around the cell and protecting it in its intertidal extreme environment. Research has revealed that Alguard® is not merely a physical barrier but an active protection against photo damaging, ageing and micro abrasion of the skin. (4)

Only a few species of microalgae have been studied and used in some commercial applications: *Spirulina, Chlorella, Haematococcus, Dunaliella, Botryococcus, Phaeodactylum,* and *Porphyridium*. For instance, colorants for cosmetic formulations such as eye shadow, face make-up, and lipstick are currently obtained from red microalgae. (103)

Bacteria

Bioactive compounds such as MAAs, carotenoids and fatty acids from microorganisms might represent a sustainable, low-cost and fast-production alternative to other natural molecules used in photo-protective, anti-aging and skin-whitening product. Specimens such as *Pseudomonas sp.* was found to produce the tyrosinase inhibitor methylene chloride, which reduced the pigmentation of human melanocytes. (1) Another great example are the *Thermus thermophilus*, a thermophilic bacteria, shows an especially adaptive physiology, enabling its survival under a great variety of conditions such as temperatures ranging from 50°C to 82°C, based on proteins, organelles, and DNA that are more resistant than those of organisms adapted to living at room temperature. (91,105)

Other Biological Sources

Fungi are abundant and ecologically relevant members of marine microbial assemblages. They were believed to be rare in marine environments, but recent studies based on molecular and metagenomics approaches have revealed an unexpected diversity from coastal to deep-sea ecosystems. Deep-sea fungi have been less described in terms of their abundance, diversity and ecological role, but are potentially important and productive sources of bioactive molecules. (79)

The marine fungus genus *Acremonium* from sponges, mangroves and seawater, was found to produce novel hydroquinone derivatives (*e. g.*, 7-isopropenylbicyclo[4.2.0]octa-1,3,5-triene2,5-diol and 7-isopropenylbicyclo-[4.2.0]octa-1,3,5-triene-2,5-diol-5-,-D-glucopyranoside) with significant antioxidant activity. The activities of these antioxidants were found to be considerably higher than the synthetic ones commonly used such as butylated hydroxytoluene. (1,106)

Coral powders have been used in numerous cosmetic products, being touted as copious and unique. It has been used to scrub skin and supplying trace minerals to it. The prospective for using fossilized coral powder as a new sustainable material for cosmetic applications is supported by its physical, chemical and textural characteristics, as well as its trace mineral content. This coral

powder is used to protect from UV radiation and acts as antioxidant, anti-ageing, and anti-acne. (41)

Phytoplankton extract, rich in lipids and omega-3 fatty acids, stimulates the cells to produce cerebrosides (pro-ceramides), strengthen cellular cohesion, renews the skin's protective barrier. Phytoplankton are very diverse. Important groups of phytoplankton include the diatoms, cyanobacteria and dinoflagellates, although many other groups are represented.
Mainly used for skin toning, skin whitening, anti-wrinkling and ageing etc. (41)

Sea water and Sea mud

Sea water contains minerals (sodium, potassium, magnesium, calcium, sulphates, and chlorides) which are beneficial for the skin. Moreover, sea salts can be used in cosmetics for skin care. Deep-sea water is as near to freezing as possible, and the pressure of the deep sea is between 20 and 1,000 atmoshpheres. The temperature is between 2 and 5 degrees Celsius and there is little light that filters down into the upper zones of the deep sea, and lower than 4,000 meters there is absolutely no light whatsoever. Hence, these different conditions would have beneficial properties on general health and especially on skin health, with a positive impact on atopic dermatitis. The health benefits are claimed to be related to the minerals, such as Mg, Ca, Cl, Na, K, Se, and V, contained in the seawater and to the quality of the deep-sea water sources. Products such as Pheohydrane® have already reached the market. (56)

Sea mud also contains various salts and minerals (*e. g.*, magnesium and sodium), and even antibacterial components (*i.e.*, Escherichia coli, Staphylococcus aureus, Propionibacterium acnes, Candida albicans rapidly lost their viability). It has been used in skin care and cosmetic product formulations for their beneficial effects and therapeutic properties on psoriasis and other skinrelated disorders. Sea mud helps to retain water, equilibrates skin pH, promotes skin repair and prevention of acne, and exhibits anti-aging properties. Also, sea mud masques stimulate, tighten, clean, and invigorate the skin with a refreshing glow. However, sea water and sea mud can contain toxic elements (*e. g.*, cadmium and lead) that occur naturally or due to pollution and must therefore be subject to strict control. Consumers must be made aware of the presence of these metals through a clear product label to avoid their use by sensitive persons. Some products as Ahava® and Erno Laszlo® have already reached the market. (20,56,107)

5. Innovative Company Mentality and Values

There are challenges in the use of marine derived bioactive compounds in cosmetic formulations. Requirements such as the level of standardization, efficacy, and traceability of marine derived products need to be met. It has become a popular practice to increase the production of bioactive components through genetic manipulation. However, due to the reduced information on genomics and gene regulation mechanisms regarding bioactive compounds, there are still major constraints and limitations hindering the development of this type of research. Thus, it may require long-term research to achieve major breakthroughs in this area. (73)

5.1 Sustainability

Sustainability is a term with multiple definitions and interpretations, but the widely accepted definition arises from the 1987 report entitled "Our Common Future" (figure 3). The idea of sustainability raised from the concept of sustainable development, meaning the ability to meet the current needs of the population without compromising future generations to meet their own needs. (36)

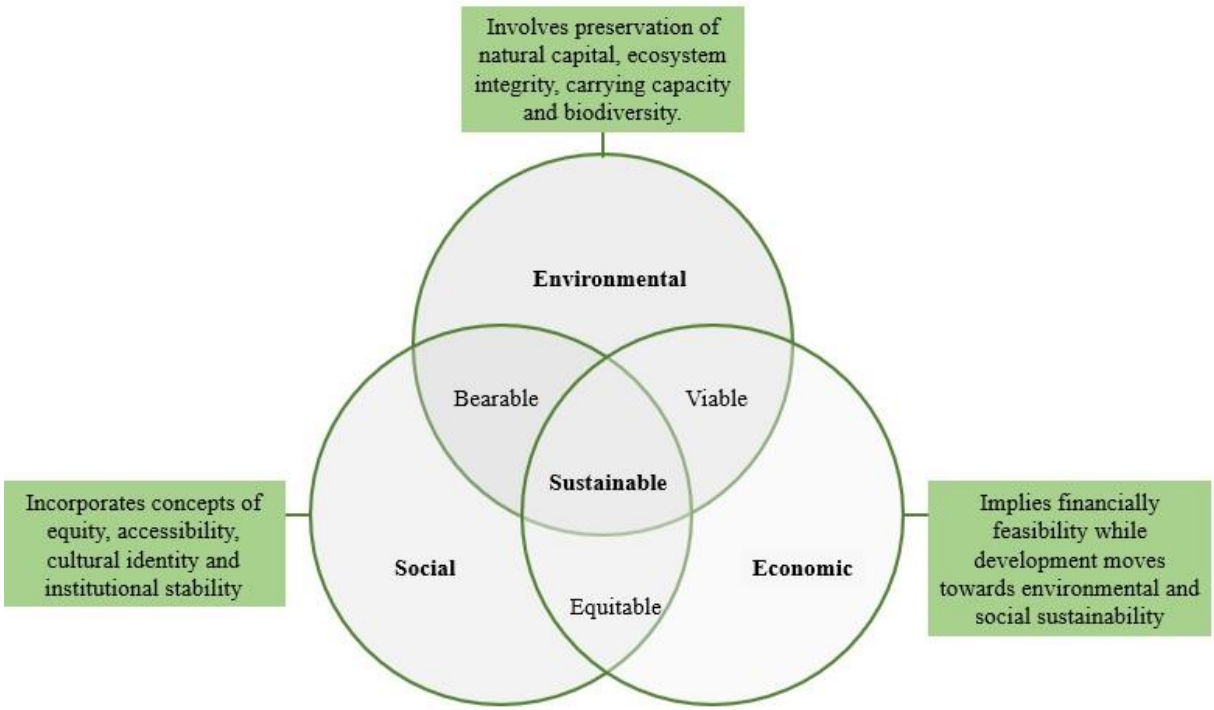

Figure 3 - Dimensions of sustainability. Adapted from (36).

Cosmetic and personal care products are used in huge quantities throughout the world; as a result of their regular use, they are continuously released into the environment in very large amounts. Many of these products are biologically active and are characterized by persistence and bioaccumulation potential, posing a threat to the ecosystem and human health. (14)

The hazard of the continuous release of these huge amounts of chemicals into waters should not be underestimated. The environmental fate of these products is largely unknown, and, if in some cases they are removed in wastewater treatment plants, in other cases, they can escape conventional treatment processes, persist in the environment at unexpected levels, undergo bioaccumulation, and even react with other pollutants to originate new unpredictable contaminants.(14) Therefore, a series of research have addressed the different types of waste and have proposed different approaches in order to minimize it, such as the use of natural ingredients that when returned to the environment will not cause as much arm. (73)

An example of this problem is in UV filters employed in sunscreen preparations and other personal care formulations. A few recent studies have shown that some of these chemicals reach

surface waters (rivers, lakes and coastal seawater), mainly during the summer, as a result of bathing while using sunscreen lotions. Besides, they have also been encountered in sewage water and sludge due to their household use in other personal care products. Finally, the lipophilic character of some of the analytes has also led to bioaccumulation in fish, sediments, and soil. (108)

Currently, the search for new marine natural products depends on the harvest of specimens from the wild whose drawback is their sustainability and replicability. Sustainability issues are associated with large amounts of biomass that are usually required for drug discovery, whereas replicability problems are related with environmental variability and community-level changes to the chemical assets of the target organisms. Individuals of the same species sampled in different geographical areas or different seasons may not contain the same chemical composition and therefore may not guarantee the supply of the target metabolite. However, recent techniques in aquaculture (*e. g.*, genetic improvement of farmed species, control of reproduction, control of viral and parasitic diseases, diet and husbandry techniques to improve disease resistance, advances in diets and environmental conditions for particular fish species aquaculture) may offer an alternative to overcome these two issues, as animal biomass can be continuously produced using homogenous environmental conditions. (73,109)

In this evolutive process, cosmetic companies face difficulties when adapting to sustainable practices. When choosing a sustainable product, the consumer expects the quality and efficacy of a "non-sustainable" alternative and this has been one of the great challenges for the cosmetic industry. Each phase of a cosmetic product life cycle will affect its sustainability. However, due to the significance of the designing phase, it is critical to address the sustainability aspects of the ingredients used to formulate such product. (36)

Economically, sustainable practices in the cosmetic industry are a demand that must be embraced in order to be successful and even viable in the long term. Acting to improve sustainability within the industry does not necessarily require big investments and it can bring many benefits to the company such as saving money, increasing sales and improving the company's reputation. (36)

5.2 Packaging

It is important to consider that preserving a packaged product depends on the characteristics of the packaging material and on the proper conditions of packaging, transport, storage, and distribution. (110) Nevertheless packaging, in general, has contributed to land and marine pollution and the excess of the materials used. (36)

The five main categories of marine debris comprise plastic, paper, metal, textile, glass and rubber. Plastics are recognized as the major constituent of marine debris, representing between 50% and 90% of the total marine debris found globally. In 2018, in the U.S. alone, almost 7.9 billion units of rigid plastic were created just for beauty and personal care products. (111,112)

Sustainably produced raw materials are being introduced into the cosmetics field not only as ingredients for cosmetics but also as components of the packaging materials. Indeed, cosmetics

marketing stresses that the use of green, possibly compostable or biodegradable packaging is an added value to the cosmetics product, since it reflects customers' and producers' environmental attitude and care. (113)

Cosmetic products are highly valuable but easily perishable and prone to contaminations. Therefore, it is important to consider preserving the packaged. (110) In the specific case of inner cosmetic packaging (figure 4), re-use is rarely applied, even chemical and mechanical recycling is not easily feasible due to difficulties in post use packaging collections, and due to packaging being often strongly contaminated by residues from the greasy and creamy cosmetic product, hard to remove by washing. In this context, the use of compostable packaging would be very beneficial for the environment, allowing for the collection of the post use packaging in the green bins. (114)

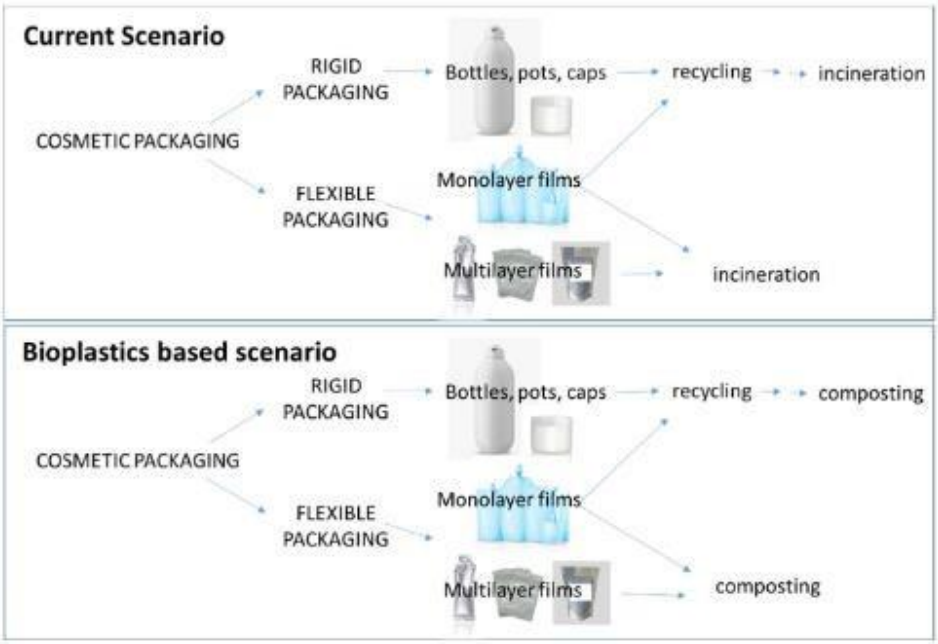

Figure 4 - General waste management of cosmetic packaging: current and bioplastics-based scenarios. From (114).

Rigid bioplastics are currently available for packaging of creams, lipsticks, etc. Several biobased and biodegradable polymers such as polyhydroxyalkanoates, polysaccharides, Poly(lactic acid) (PLA), bio-PE, or bio-PET are mainly used. However, the market and the specific cosmetics field require not only bio-based, biodegradable or recyclable materials, but also bioplastics since their improvements in functionalities target the specific application. Indeed, special requirements are necessary for cosmetics packaging, due to the intrinsic instability of cosmetic products. (114,115)

The goal is to achieve zero-waste packaging, in which every part of the packaging is reusable or recyclable, meaning that no actual waste is generated. This could mean that the packaging is meant to be used for another purpose by the consumer on the other end, like an edible

container, “plantable” paper embedded with seeds, or packages that can be returned to local dropoff points for re-use. (7) Some innovative sustainable packing materials include the following:

- Bamboo, which is the fastest growing plant in the world, making it the number one renewable resource.
- Compostable/biodegradable paperboard is made from recycled paper pulp. When manufactured and disposed of properly, it is largely considered a renewable resource. E.g., bottle of recycled paper, resistant to water, with inner layer of plastic.
- Glass and metal are 100% recyclable. This means that they can be infinitely recycled into new packaging without loss of quality. Ex. Aluminium tube or recycled glass and soy-based lid.
- Recycled plastic is another option. Many companies repurpose plastic into new packaging.
- Cork, which is a renewable or sustainable material because the harvesting of cork doesn't require the cutting down of any trees. In addition, it can be recycled and/or repurposed.
- Rubber. There are different types of rubbers (natural, synthetic, recycled and reclaimed). Not all are 100 percent environmentally friendly, the recommended rubber is the procured from plants that features latex. Synthetic rubber enjoys the same properties, but the production is very different.
- Polyethylene Terephthalate (PET) packaging. PET is a remarkably energy-efficient packaging material. Add to that its strength, versatility, and recyclability, and PET boasts an excellent sustainability profile.

And sometimes less is more so, no second packaging unless strictly necessary for stability. (7) Reusable packaging is another effective measure and some cosmetics companies are already opting for long-lasting packaging that can be refilled. (36)

An ascending marine sourced packaging and front-runner in edible packaging materials is seaweed. It is naturally high in fibre and vitamins and can be turned into packaging without the need for chemicals, plus seaweed does not need water, fertilisers or other key resources to grow, and absorbs CO_2 as it does. The material is being looked at for wrapping for sandwiches, burgers and other snacks, as well as to replace plastic sachets for instant coffee and noodle seasoning.(116)

5.3 Safety Concerns and Regulations – European scenario

From a regulatory standpoint, cosmeceuticals are simply cosmetics thus legal framework of cosmetics can be transposed to cosmeceuticals as well. (11) The shared information should be uniform in all states of CEE. Here, CosIng is the European Commission database for information on cosmetic substances and ingredient. (84)

The key principle of the Cosmetics Regulation in the EU market is that the person or company who places the cosmetic product on the market is responsible for that product (so called

'Responsible Person'). It is the responsibility of that person or company (usually the manufacturer or the importer) to ensure that the product is safe and meets all the requirements (from the choice of ingredients to the placing on the market of the product) of the Cosmetics Regulation. (53)

Under the Cosmetics Regulation, the system of cosmetovigilance, whereby serious undesirable effects must be reported to the Responsible Person and relevant authorities, ensures that the safety of cosmetic products placed on the EU market is monitored throughout Europe. (53)

Companies and competent authorities are also engaged in monitoring the safety of products on the market by performing appropriate checks on cosmetic products and companies manufacturing, marketing and retailing of those products. Member states must also monitor compliance with the principles of good manufacturing practices. (53) Reviews and assessments of the work of the market surveillance authorities must be carried out at least every four years. (3)

Quality control and standardization of cosmetic products are crucial to ensure the safety, efficacy, and quality of products and its raw material. It is essential to evaluate the presence of heavy metal like arsenic, mercury, lead and cadmium, pesticides, such as organochlorine, allergens, toxins, and other chemical contaminations in the samples. The level of contaminations must be low, as set by the World Health Organization and USFood and Drug Administration. One of the precautions to be considered in developing cosmetic products is that certain drugs have side effects of phototoxicity. This is due to the presence of phototoxin or photoallergen, which is activated following skin contact and light exposure, known as phytophoto contact dermatitis. Thus, a clinical study has to be carried out to determine the safety and efficacy of these compounds in humans. (49)

5.4 Risks of Marine based Cosmetics Commercialization in Mass Market

Supply and Technical Challenges

Several challenges arise associated with ensuring continuous large-scale production of a bioactive compound for trials, and most importantly for continuous supply to the market. (47)

The first one is related to the variability of the organism itself. For instance, taking the example of sponges, the high frequency of their bioactive metabolites is interpreted as chemical defence against environmental stress factors such as predation, overgrowth by fouling organisms or competition for space. The highest incidence of toxic or deterrent sponge metabolites is found in habitats such as coral reefs that are characterized by intense competition and feeding pressure. Because these environmental conditions are not static, it is likely that a resupply of the same organism does not provide the same metabolite. Also, in the case of marine invertebrates another challenge is the fact the microorganisms are sometimes the actual producers of the bioactives. Once a particular natural product has been isolated and identified as a lead compound, the issue of its sustainable supply is faced. (90)

Most of the times, the compound of interest is present only in low amounts and/or can be very difficult to isolate. In the case of tissues of marine invertebrates, which present unique extraction-related problems due to their high water and salt content, this problem can be even more challenging. Whatever the intended use of the bioactive compound, several to hundreds of grams

are required for preclinical development, several kilograms are needed for clinical phases and tons for commercial uses. Mariculture (farming the growth of the organism in its natural milieu) and aquaculture (culture of the organism under artificial conditions) have been attempted, however, the unique and sometimes exclusive, conditions of the sea make cultivation very difficult and often impossible. This lack of sustainable supply of substances has stopped further development of several highly promising marine compounds, and attempts have been made to overcome this barrier by developing synthetic or hemisynthesic analogues, derivatives with more manageable properties, or by design of a pharmacophore of reduced complexity which can then be synthesized. However, it is worth noting, that these approaches embrace themselves their own challenges. Total synthesis is by no means an easy undertaking task, and chemistry still has a very long way to go before it can make any molecule in a practical manner. Hemisynthesis may be, in some cases, a good solution for bioactive compound‘s supply. This process involves harvesting a biosynthetic intermediate from the natural source, rather than the lead itself, and converting it into the lead. This approach has two advantages. First, the intermediate may be more easily extracted in a higher yield than the final product itself. Second, it may allow the syntheses of analogues of the final product. (7)

Challenges Faced during Marine Natural Products Development

The access to the ocean and to the deepest of its spots remains very difficult and further robotic and engineering technology is needed to fully evaluate the oceans available biodiversity. However, the developments of SCUBA diving techniques clearly improved the capability to access deeper ocean floor and further the finding of more fascinating marine natural products. (32,43)

Marine natural product studies were formerly conducted, randomly, in shallow coastal waters, which left aside an enormous community of very promising organisms which lived in untapped but unreachable environment, e.g., hydrothermal vents and sea mounts. Sampling in difficult access spots, deeper than 30 m, is not possible by scuba diving and is usually performed by trawling. This technique besides being unselective, often damages the samples and the benthic ecosystems, and hides valuable information about the environment of the organism. The ideal sampling of marine organisms in deep waters is using sophisticated or ingenious equipment, such as manned submersibles and, more recently, remotely operated vehicles (ROVs) that allow us to observe the organism‘s habitat. Unfortunately, these sampling facilities are very expensive and only a small number of laboratories have access to them, a drawback that is difficult to overcome, especially if we think that most of the biological diversity is located in underdeveloped countries from the tropical and subtropical regions. This is just one of the reasons why international collaboration is so important in this research field. (1,7,32)

Despite the differences between pharmaceutical, nutraceutical and cosmeceutical segments, they are all mined with serious bottlenecks that can be divided into three major areas: biodiversity access, supply and technological issues and market barriers.(117)

Market Challenges

Finally, the commercial and market issues are very relevant and most of the times disregarded in the natural product development programs. Since the very early stages of the development programs, several very important questions must be addressed by the researchers or the companies (Figure 5). (1,7)

The high number of natural products hits and leads coming out of the High-throughput screening (HTS) technologies has stressed out the need for a focused strategy on this field, otherwise the risk of failing and running out of cash fast is high, especially in the case of Small and Medium Enterprises. It is crucial to be aware that the cost of the technology and manufacturing processes, sometimes with poor yields, raises the market cost per kilogram and may render these products economically unviable. This is particularly true in personal care industry where recombinant technologies are not acceptable and the profit margins are too small to introduce very expensive ingredients per pack. (1,7)

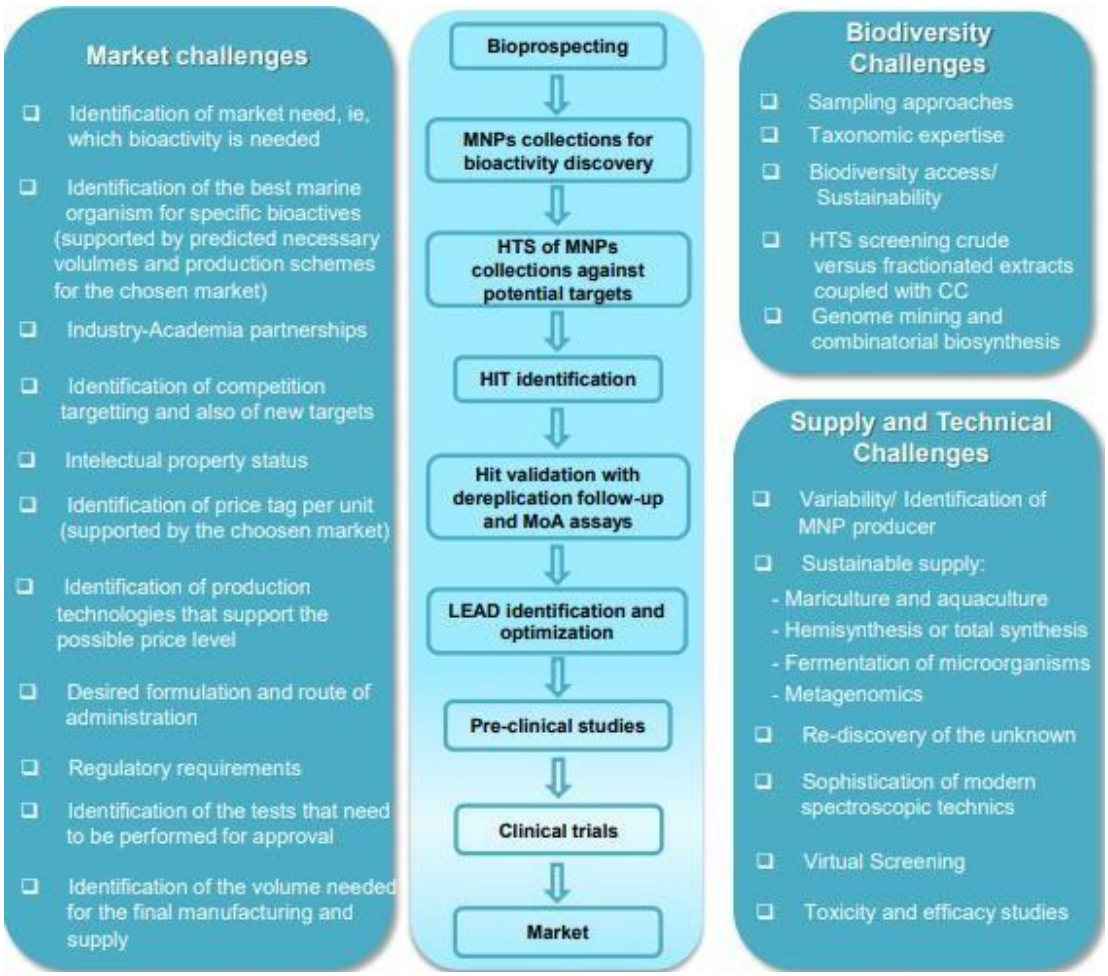

Figure 5 - Marine Natural Products: from bioprospecting to market, highlighting biodiversity, supply and technical and market challenges faced during the process. From (7).

6. Conclusion

Consumers' demand is turning to natural products, forcing research to uncover alternative sources of bioactive cosmetically active molecules. This dissertation explores the use of marine organisms, such as macroalgae and bacteria, as potential source of bioactive compounds for cosmetics. The variety of molecules and compounds described in this research highlight the marine environment as an underexploited resource, especially for deep sea-inhabiting marine organisms that remain to be described. Once the valuable species are clearly identified, it will remain to optimize the mode of extraction of the molecules of interest and to perform tests to ensure their effectiveness and their safety for cosmetic applications. The applications of marine products are endless. The bioactive compounds can increase protection against UV exposure, prevent skin cancer, improve skin condition and prevent skin aging. We should also view these ingredients as pure and innovative compounds, as there is no terrestrial equivalent and, thereupon, they will without a doubt bring benefits. As a future perspective, a fruitful cooperation among researchers and industries will drive the cosmetic sector toward being more ecological by responsible sourcing of ingredients, implementing earth-friendly manufacturing processes, and experimenting with inventive recycling and reuse programs, therefore contributing to save our environment. We, the consumer should acknowledge that the tiniest gestures make an impact.

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