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REVIEW ARTICLE

Marine algae as attractive source to skin care

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ABSTRACT

As the largest organ in the human body, the skin has multiple functions of which one of the most important is the protection against various harmful stressors. The keratinised stratified epidermis and an underlying thick layer of collagen-rich dermal connective tissues are important components of the skin. The environmental stressors such as ultraviolet radiation (UVR) and pollution increase the levels of reactive oxygen species (ROS), contributing to clinical manifestations such as wrinkle formation and skin aging. Skin aging is related to the reduction of collagen production and decrease of several enzymatic activities including matrix metalloproteinases (MMPs), which degrade collagen structure in the dermis; and tissue inhibitor of metalloproteinases (TIMPs), which inhibit the action of MMPs. In addition to alterations of DNA, signal transduction pathways, immunology, UVR, and pollution activate cell surface receptors of keratinocytes and fibroblasts in the skin. This action leads to a breakdown of collagen in the extracellular matrix and a shutdown of new collagen synthesis. Therefore, an efficient antioxidants strategy is of major importance in dermis and epidermis layers. Marine resources have been recognised for their biologically active substances. Among these, marine algae are rich-sources of metabolites, which can be used to fight against oxidative stress and hence skin aging. These metabolites include, among others, mycosporine-like amino acids (MAAs), polysaccharides, sulphated polysaccharides, glucosyl glycerols, pigments, and polyphenols. This paper reviews the role of oxidative processes in skin damage and the action of the compounds from algae on the physiological processes to maintain skin health.

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Introduction

Skin is the largest and one of the most complex organs representing one sixth of the total body weight. It functions as a physical barrier to protect the body from water loss as well as environmental insults such as pathogens, chemicals, physical agents, and solar ultraviolet radiation (UVR) throughout the life. It provides essential physiological functions including immune defence, thermoregulation, sensory input from mechanoreceptors, endocrine and metabolic mechanisms to sustain optimal health.

Skin aging is a slow and complex process including intrinsic and extrinsic mechanisms inducing many changes such as thinning, dryness, laxity, fragility, enlarged pores, fine lines, and wrinkles [1,2]. Intrinsic aging occurs as a natural consequence of physiological and genetic changes. Extrinsic aging is caused by cumulative exposure to external stimuli such as UVR, pollution, and infectious agents that induce DNA alterations and damage to the skin. UVR, in particular ultraviolet A (UVA) and ultraviolet B (UVB), is the most harmful external component threatening the skin and, for this reason, extrinsic aging is also referred to as photoaging. Based on their distinct physical properties, these components of sunlight penetrate into the skin and interact with different cells that are located at different depths, inducing distinct overlapping biological responses in both the epidermal and dermal layers. Reactive oxygen species (ROS), arising from oxidative cell metabolism, cause damage to cellular components such as cell walls, lipid membranes, mitochondria, and DNA, playing a major role in both process. Figure 1 summarises various ROS formation pathways.

Molecular mechanisms of skin aging can induce inflammatory response, stimulate mitogen-activated protein kinases (MAPK) involved in the phosphorylation of transcription factor activator protein 1 (AP-1), which, in turn, results in upregulation of metalloproteinases

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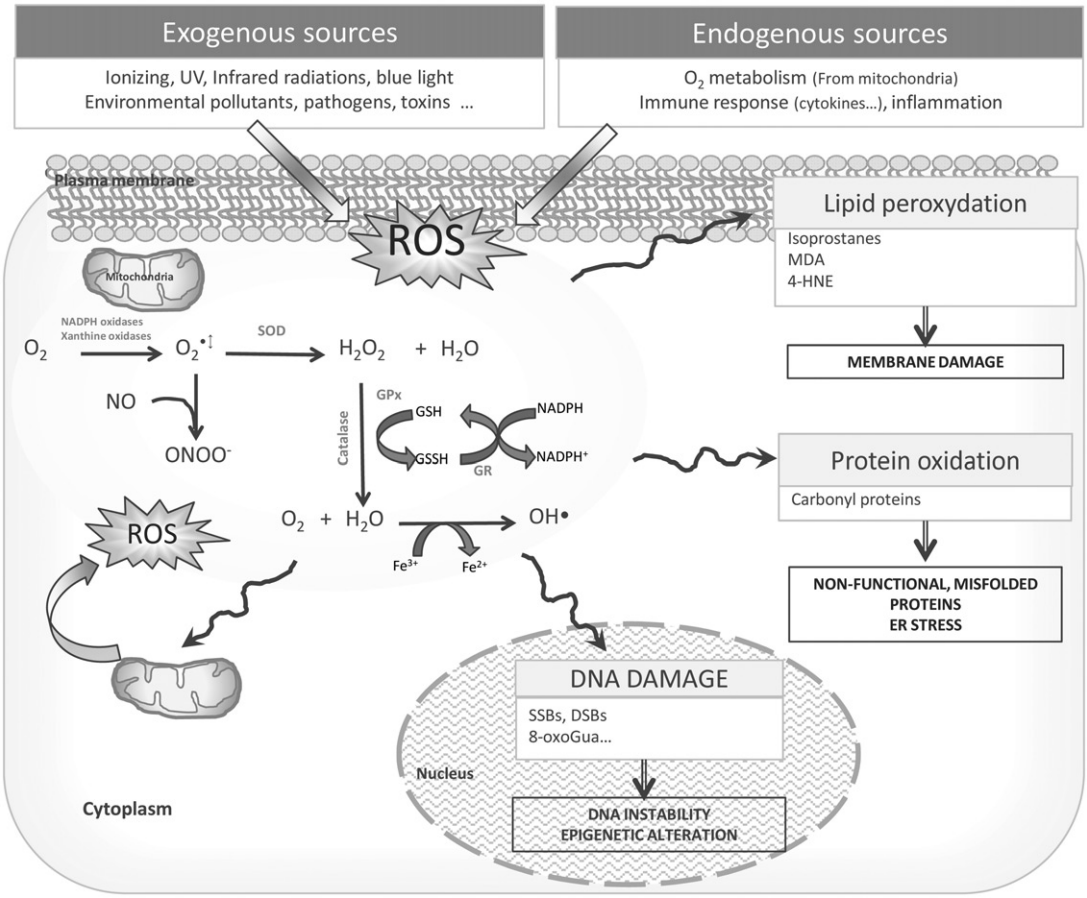

Figure 1. ROS-induced cellular damage. Skin cells are continuously exposed to exogenous and endogenous sources of ROS. Mitochondria or enzymes such as NADPH oxidase or xanthine oxidase are endogenous sources of ROS. The cell is equipped with a variety of defence mechanisms to scavenge ROS. SOD catalyse the dismutation of superoxide into hydrogen peroxide. Catalase (CAT) reacts with the hydrogen peroxide to catalyse the formation of water and oxygen. Glutathione peroxidase (GPx) reduces hydrogen peroxide. Reduced GSH is converted to oxidised glutathione (GSSG) during which H_2O_2 is converted to water. Damaged mitochondria produce more ROS in a vicious circle. Single and double strand breaks (SSBs, DSBs); 8-oxo-7,8-dihydroguanine (8-oxoGua); Malondi-aldehyde (MDA); and 4-hydroxy-2-nonenal (4-HNE).

(MMPs: MMP-1, MMP-3, and MMP-9) contributing to the degradation of skin collagen and connective tissue [3]. Wrinkle formation is one of the primary characteristics of skin aging, and is a complex process that involves age-dependent decline of skin cell function. Collagen makes up to 70–80% of the dry weight of skin and contributes to the stability and structural integrity of tissues. The major cause of wrinkles is a loss of structural protein (type-1 collagen) in the dermal layer of the skin. MMP-1 and elastase enzymes are responsible for the breakdown of various components of the extracellular matrix (ECM), i.e. collagen and elastin. Thus, wrinkles result from a combination of intrinsic and extrinsic aging as well as increased levels of MMP-1 and elastase enzymes. Compounds able to increase MMP inhibitory activities, hyaluronidase inhibitory activity, expression of collagen and elastase inhibitory activity may have the potential to be used as an active ingredient in new anti-wrinkle cosmetic products.

The goal is to delay aging onset and/or slow down the structural and visual appearance of skin aging with time, through the neutralisation of ROS overproduction. Biological responses are characterised by the upregulation of antioxidant enzymes and decreased sensitivity to oxidative damage [4]. The cosmetics industry has focussed on bioactive substances derived from natural products such as plants, microbial metabolites, mushrooms, and marine algae. This attention is due to the presence of antioxidants preventing photoaging and their low toxicity effects [5]. In addition, the increasing demand of consumers for natural and sustainable products, has reinforced emerging developments based on such products [6,7]. With tens of thousands of varieties in the world, seaweed constitutes a major reservoir of bioresources with multiple applications. Compared to the terrestrial plants, seaweed is rich in some health-promoting molecules and materials such as polyunsaturated fatty acids, essential amino acids, vitamins A, B,

C, and E, antioxidants and immunologically effective compounds, which are essential for cosmetic product developments [8]. Many marine organisms live in complex habitats exposed to extreme conditions. In adapting themselves to new environments, they produce a wide variety of secondary (biologically active) metabolites which cannot be found in other organisms. For example, pigments from algae like phycobiliproteins are very original and absolutely not present in land plants. Moreover, considering its great taxonomic diversity, investigations related to the search of new bioactive compounds from the marine environment can be seen as an almost unlimited field. Thus, the marine environment is much richer in its biodiversity, thereby making marine organisms and their metabolites unique. More precisely, a number of photoprotective compounds such as scytonemins, mycosporine-like amino acids (MAAs), and several other UV-absorbing substances have gained much importance in cosmetic product developments.

Many algae metabolites and pigments have antiaging, antioxidant, and neuroprotective properties, making them suitable for use in cosmetics. Thus, in the present review, marine algae compounds have been discussed toward cosmetic applications. The main sections of this review include the mechanisms of the extrinsic skin aging resulting from exposure to UV and pollution and the potential of marine algae-derived compounds to fight against this phenomenon via reducing oxidative stress cascade events.

Skin aging and ROS

Photoaging of the skin occurs mainly due to UVR and pollution.

UVR

In addition to direct DNA alterations, which include DNA base damage, DNA single- and double-strand breaks, and cross-linking of DNA and proteins, UVR-generated ROS modulate the MAPK, the nuclear factor-kappa beta (NF-κB), and the nuclear factor erythroid 2-related factor (Nrf2). Altogether these factors play important roles in skin photoaging by the regulation of transcription and activity of genes related to cell proliferation, differentiation and survival as well as tissue remodelling. Moreover, repeated doses of UVB stimulate various signalling pathways that end up by activating the p53/p21 and/or p16 growth-suppressive pathway and the combined level of activation of both pathways, able to determine the onset of senescence.

More precisely, the activation of MAPK pathway such as extracellular signal-regulated kinase (ERK), p38, and c-Jun-N-terminal-kinase (JNK) results in the activation of transcription factor AP-1, which together promote the expression of MMPs, such as MMP-1, MMP-9, and MMP-3, inducing collagen degradation (Figure 2). MMPs are activated in two ways: 1) ROS inhibit tissue inhibitor of matrix metallo-proteases (TIMP). The decrease in TIMP is sufficient to activate MMPs; 2) secondarily ROS, via transcription factors, activate the expression of genes encoding MMPs. The imbalance between the levels of MMPs and TIMPs is accentuated; the matrix in the dermis is degraded in this way [9]. It should be noted that transforming growth factor β (TGF-β) is the predominant regulator of MMPs that remodel the ECM during skin photoaging [10]. It appears that UVB irradiation alters TGF-β signalling pathway in human dermal fibroblasts via AP-1 transcription factor activation, mainly by decreasing the synthesis of TGF-β receptor II (TβRII) [11].

UVR also induces proinflammatory genes, inflammation being an important mediator of photoaging. Keratinocytes, fibroblasts, leucocytes, and the endothelial lining of blood vessels release inflammatory mediators such as fibrin, prostaglandins, cytokines (interleukin-1 (IL-1)), IL-6, and tumour necrosis factor (TNF-α). ROS also activate cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2). The inflammatory cascade triggers ROS.

The NFκB pathway is also activated by ROS. NFκB is a key transcription factor composed of two subunits, p50 and p65, that regulate higher oxidative stress by coordinating a proinflammatory response. NF-κB is sequestered in the cytosol by inhibitor protein IκB. The release of NF-κB requires the phosphorylation of IκB by cytosolic protein IKKβ, inducing its releasing for nuclear translocation. NF-κB mainly stimulates the expression of numerous proinflammatory cytokines such as TNF-α, IL-1α, IL-1β, IL-6, IL-8, IL-10, inducible nitric oxide synthase (iNOS), and COX-2, responsible for the synthesis of the inflammatory mediator PGE2.

Additionally, in the *stratum corneum*, trans-urocanic acid (UCA), generated through the degradation of filaggrin, is converted by UV radiation into *cis*-UCA, which in turn has been demonstrated to be a key mediator of UV-induced immuno-suppression. Once converted to *cis*-isomer, UCA induces generation of ROS and up-regulates many oxidative stress-related genes within human keratinocytes. ROS generated by *cis*-UCA transiently activate the epidermal growth factor receptor (EGFR). Subsequent activation of the downstream ERK and p38 MAPK signalling pathways leads to increased transcription of COX-2 which then stimulates PGE2 release.

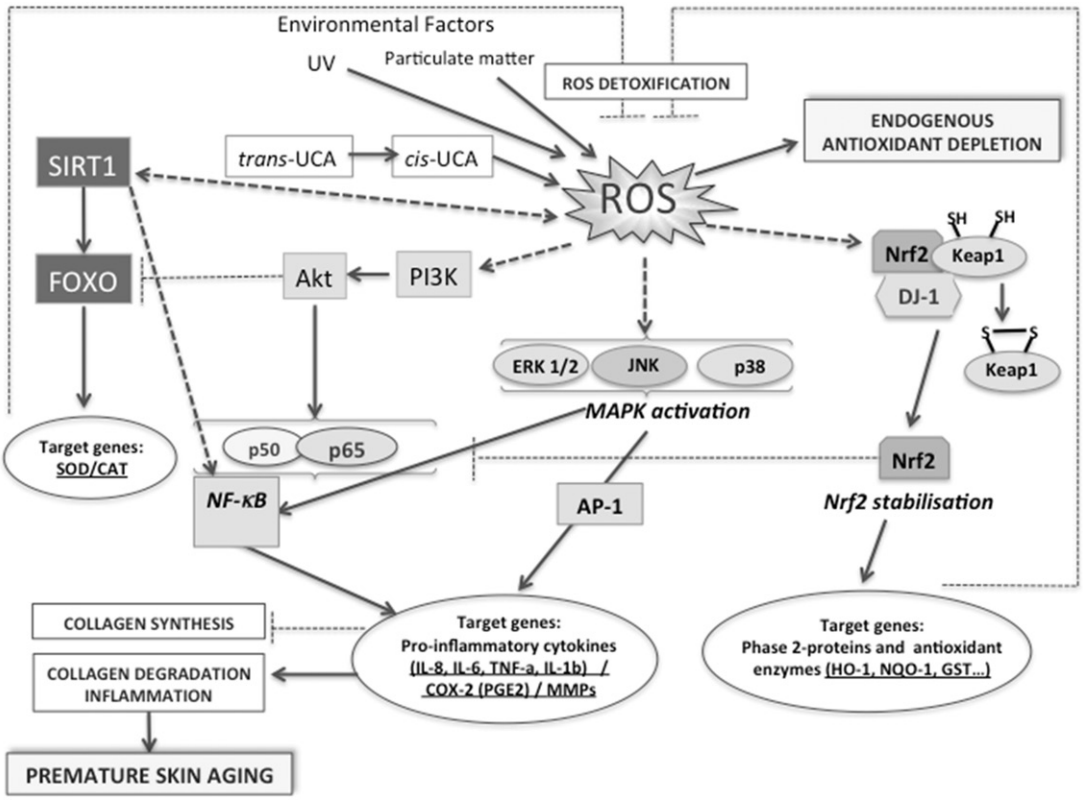

Figure 2. ROS activate several signalling pathways. Oxidative stress activates PI3K/Akt pathway that inactivates FoxO, leading to limited expression of endogenous antioxidants, such as expression of SOD and catalase (CAT). Low-level increases in ROS induced by environmental stimuli such as low doses of ionising radiation or chemicals, activates beneficial cellular responses, including Nuclear factor(erythroid-derived two)-like 2 (Nrf2) activation. Under normal conditions, Nrf2 localises in the cytoplasm where it interacts with the actin binding protein, Kelch-like ECH associating protein 1 (Keap1), and is rapidly degraded by the ubiquitin–proteasome pathway. Signals from ROS or electrophilic insults target the Nrf2–Keap1 complex, dissociating Nrf2 from Keap1. The Parkinson's-associated protein, DJ-1, is indispensable for Nrf2 stabilisation, by affecting Nrf2 association with its inhibitor Keap1. Stabilized Nrf2 translocates to the nuclei, binds to the ARE and thereby regulates the expression of a large battery of genes involved in the cellular antioxidant protection, including NADPH quinine oxyreductase (NQO-1), HO-1, GSH … ROS can also activate gene transcription via transcription factors, such as NF-kB and AP-1 that can interact directly with specific DNA motifs on promoters of target genes. The transcriptions of several MMP family members are strongly regulated by NF-kB and AP-1. Increased activities of AP-1 and NF-kB lead to collagen breakdown, the downregulation of type I procollagen, and upregulations of MMPs resulting in premature skin aging. At the stratum corneum level, cis-urocanic acid (UCA) is formed by photoisomerization of trans-UCA. cis-UCA induces intracellular ROS that initiate translation of genes associated with immunosuppression and apoptosis. AKT/PKB (protein kinase B) kinase; MAPK; NF-kB: nuclear factor kB; AP-1: activator protein-1; PI3K: phosphoinositide 3-kinase; UCA: urocanic acid.

At higher concentrations, *cis*-UCA activates caspase-3 via intracellular ROS generation that down-regulates EGFR, resulting in apoptosis (Figure 2).

Increase in skin temperature

Solar infra-red radiation (IR) transmits heat energy that is responsible for raising skin temperatures. Heat-related skin damage is characterised by an increased expression of MMPs, more specifically MMP1, MMP-3, and MMP-12, resulting in the destruction of collagen and elastin [12]. Heat also induces dermal expression of tropoelastin while decreasing fibrillin-1 levels, resulting in the accumulation of elastotic material. Increased ROS production by heat is mainly due to the activation of NADPH oxidase, xanthine oxidase, and the mitochondrial electron transport system, inducing protein and DNA oxidation. It has been shown that the transient receptor potential vanilloid-1 (TRPV-1) activated by heat mediates the expression of MMP-1, opening a potential role for TRPV-1 inhibitors to be used to prevent heat-induced skin aging [13].

Pollution

Air pollution is another major environmental cause of ROS production. The human skin is one of the first and major targets of air pollutants due to its peculiar

location [14]. Particulate matter (PM), which includes the harmful suspended contaminants in the air, is generally encompassed in air pollution. It appears that PM affects the development and exacerbates the skin pathologies [15]. PM includes the suspended contaminants in the air such as particulate contaminants (tobacco smoke, soot…), various types of dust, biological contaminants (pollen), and gaseous contaminants (exhaust gas from traffic). PM also comprises sulphates, nitrates, and polycyclic aromatic hydrocarbons (PAHs). One of the mechanisms associated with the adverse effects of PM on skin diseases is the increased generation of oxidative stress and the proinflammatory reactions induced by PM, such as increase in TNF-α, IL-1α, and IL-8, from human keratinocytes [14,16].

In urban air pollution, PAHs, which are potentially carcinogenic, coexist with PM in environmental complex mixtures. Ambient PAHs mixtures are mainly derived from coal tar, diesel exhausts, and cigarette smoke. The absorbed PAHs contribute to carcinogenesis by interacting with a specific receptor, AhR, which is known as a transcription factor. Interaction between PAHs and AhR induces PAHs-mediated carcinogenicity in many kinds of cells by generating numerous carcinogenic metabolites. Generally speaking, AhR can be described as a general mediator of environmental stresses, especially in terms of mitigating damage from ROS, changes in oxygen levels, and inflammation. In regulating the responses to these stresses, AhR is critical to normal cellular function and affects many important processes in cell proliferation and differentiation. AhR's role as a mediator of cellular stresses can be partially explained by its interactions with HSP90, a molecular chaperone known to regulate protein function in order to allow cells to adjust to intra- and extracellular stresses.

One of the leading contributors to outdoor air pollution is also ozone (O_3), formed by the interaction of sunlight with air pollution, particularly hydrocarbon motor vehicle exhaust emissions. Its toxic effect has been shown to be mediated through free radical reactions that lead to the oxidation of biomolecules, and subsequent formation of radical species together with the production of cytotoxic molecules such as aldehydes and more general peroxidation products. Valacchi et al. reported that O_3 exposure induces a cascade of cellular stress responses in deeper cellular layers of the skin [17]. It reacts quickly and has been found to deplete antioxidants in murine skin and to increase cytochrome P450 enzymes in normal human epidermal keratinocytes. Human epidermal keratinocytes responded to O_3 exposure by a proinflammatory response, inducing an increase in IL-1α, a release that may trigger the immune function of the skin and may induce further damage and, thus, accelerates the aging of skin. O_3 exposure demonstrated a dose-dependent increase in p65 subunit nuclear expression as a marker of NF-κB activation; the activation of NF-κB may be accomplished via accumulation of ROS promoting dissociation of NF-κB from its cytoplasmic repressor IκB [18]. Moreover, the levels of peroxidation products in keratinocytes are not homogenously distributed in the skin tissues, but its formation follows a gradient dispersion where higher levels are present in the most external layer [18]. Thus, it seems useful to protect the skin from the deleterious effects of O_3, especially since cutaneous tissue is one of its primary targets. The use of protective antioxidant mixtures with proven ability to neutralise the pro-oxidant effect of pollution, appears to be recommended to maintain the healthy integrity of the skin.

Skin protection mechanism

Increased amounts of ROS stimulate cells to activate different mechanisms of defence, including the induction of a battery of antioxidant genes and phase II detoxifying enzymes, the thioredoxin system, the peroxiredoxin family as cellular antioxidants, and low molecular weight antioxidants [18].

Nonenzymatic antioxidants include a variety of free radical quenchers such as ascorbic acid, alpha-tocopherol, carotenoids, flavonoids, thiols which include glutathione (GSH), ubiquinone Q10, uric acid, bilirubin, ferritin, albumin, transferrin, lactoferrin, and micronutrients which act as enzymatic cofactors.

At the molecular level, cellular stress response pathways are controlled by four categories of molecules and transcriptional regulators: insulin/IGF-1 signalling, sirtuins, target of rapamycin, and AMP-activated protein kinase (AMPK)-dependent pathways. All these pathways have one molecular target in common, named FoxO1. FoxOs are redox sensitive Forehead-containing ubiquitous transcription factors, and represent a major cell defence mechanism against oxidative insults [19].

Nrf2 is a transcription factor which is the key to protection against oxidative stress. It regulates not only a variety of antioxidant enzymes, such as NAD(P)H: quinone oxidoreductase (NQO1), γ-glutamylcysteine synthetase, thioredoxin, or haem oxygenase-1, but also several phase I and phase II drug metabolising enzymes, for example, UDP-glucuronosyltransferase 1A6 (UGT1A6) and glutathione S-transferase. More precisely, Nrf2 regulates phase-II protective enzymes which are responsible for the antioxidant response, xenobiotic disposition, inflammatory response, metabolic programming and cell proliferation and survival, through the antioxidant-response element (ARE). The involvement of the Nrf2

pathway in skin, is of high importance; playing a role in skin homeostasis and skin renovation [20].

Activity of Nrf2 is regulated by various mechanisms. Under homeostatic conditions, Nrf2 is generally localised in the cytoplasm, where it is sequestered by its inhibitor, Kelch-like ECH-associated protein 1 (Keap1). In response to ROS, Keap1 acts as a molecular sensor and undergoes chemical modifications in a series of reactive cysteine residues, allowing the release of Nrf2, which escapes from degradation and translocates to the nucleus, where it recruits the small Maf (sMaf) protein and binds to the ARE, a *cis*-acting DNA regulatory element that activates the promoter region of several genes encoding phase II detoxification enzymes and antioxidants. Results obtained from human fibroblasts showed that Nrf2 is modulated in response to UVA, and that low UVB doses stimulate Nrf2 transcriptional activity [21]. Additionally, Nrf2 is stabilised by DJ-1, a multifunctional protein that acts as an antioxidant and a transcriptional regulator [22]. Ooe et al. have reported increased sensitivity of DJ-1 to oxidative stress–induced oxidative modifications that destabilises and decreases functional DJ-1 protein [23]. Disruption of DJ-1 decreased Nrf2 protein stability, whereas overexpression of DJ-1 restored protein stability by decreasing ubiquitination of Nrf2. Thus, DJ-1 mediates its antioxidant effects by the Nrf2 pathway through the stabilisation of Nrf2, by interfering with Keap1-mediated proteasomal degradation. Ishiwatari et al. found that DJ-1 plays a significant role in protection against UVR and oxidative stress into the skin. Moreover, DJ-1 levels in the *Stratum Corneum* might be an indicator of antioxidative defence against UV-induced damage [24].

The aim to slow down the skin aging process needs to include not only lifestyle changes but also treatments allowing decreased ROS in order to delay the onset/development of damaged cutaneous elements. Over the past few decades, marine algae have emerged as an important source of production of a variety of secondary metabolites possessing different biological activities. In fact, marine algae are a source of many bioactives such as phlorotannins, carotenoids, polysaccharides, and MAAs. Cosmetics have a particular interest regarding the beneficial effects on skin health. Pollution and UVR have made the problem of early skin aging prominent. In the next section, the importance of marine algal metabolites is discussed for their cosmetic potential in skin care.

Bioactives substances from algae

The world of algae offers a tremendous and relatively untapped biodiversity in term of biology, physiology, and metabolism. Indeed, whereas few green algae colonised the emerged land hundred millions of years ago, the largest part of the world plants remained in the sea with unknown biologies in an aggressive aquatic world and with a very peculiar relationship to the sunlight as the energy provider, but also as a foe against which defence mechanisms had to be set up and adapted. These mechanisms are rather ubiquitous among the three usually described branches of macroalgae (seaweeds), i.e. green (Chlorophyceae), red (Rhodophyceae), brown (Phaeophyceae) on the basis of their pigmentation, brown algae accounting for 60% of the total macroalgae cultivated in the world, green algae representing less than 1% [6]. Green algae can absorb a huge amount of light energy, while red and brown algae cannot, as they live in deeper waters where there is insufficient sunlight.

Microalgae are a diverse group of microorganisms comprising eukaryotic photoautotrophic protists and prokaryotic cyanobacteria (blue algae) [25], the latter being the most important and dominant microflora. It has been reported that microalgae extracts protect the skin through the inhibition of UVR-induced gene upregulation [26]. For example, microalgae such as *Chlorella, Dunaliella*, and *Arthrospira* appear to act on the epidermis to erase vascular imperfection, boost collagen synthesis, and possibly prevent wrinkle formation [27].

The application of algae based on their valuable bioactive chemical constituents in cosmetics includes MAAs, polysaccharides, sulphated polysaccharides, glucosyl glycerols, pigments (scytonemin, phycobiliproteins, carotenoids), lipids, and polyphenols (Figure 3). Table 1 reports some of the marine sources containing bioactive compounds, which can be used in cosmetic applications.

Polysaccharides

Besides proteins and nucleic acids, marine algae are also documented to contain large amounts of Polysaccharides (PS) such as ulvans (green algae), fucoidans (brown algae), and galactans (red algae). Loose random coils or rigid helices are the two forms of PS, which can exist in solution [28]. The biological and pharmacological activities of PS normally result from a complex interaction of several structural features, including the sulfatation level, distribution of sulphate groups along the polysaccharide backbone, molecular weight, and sugar residue composition. PS exhibit many beneficial cosmetics effects.

PS from macro- and microalgae have, since a long time ago, demonstrated their biological activities: (i) enhancing the immunity (for example, for red

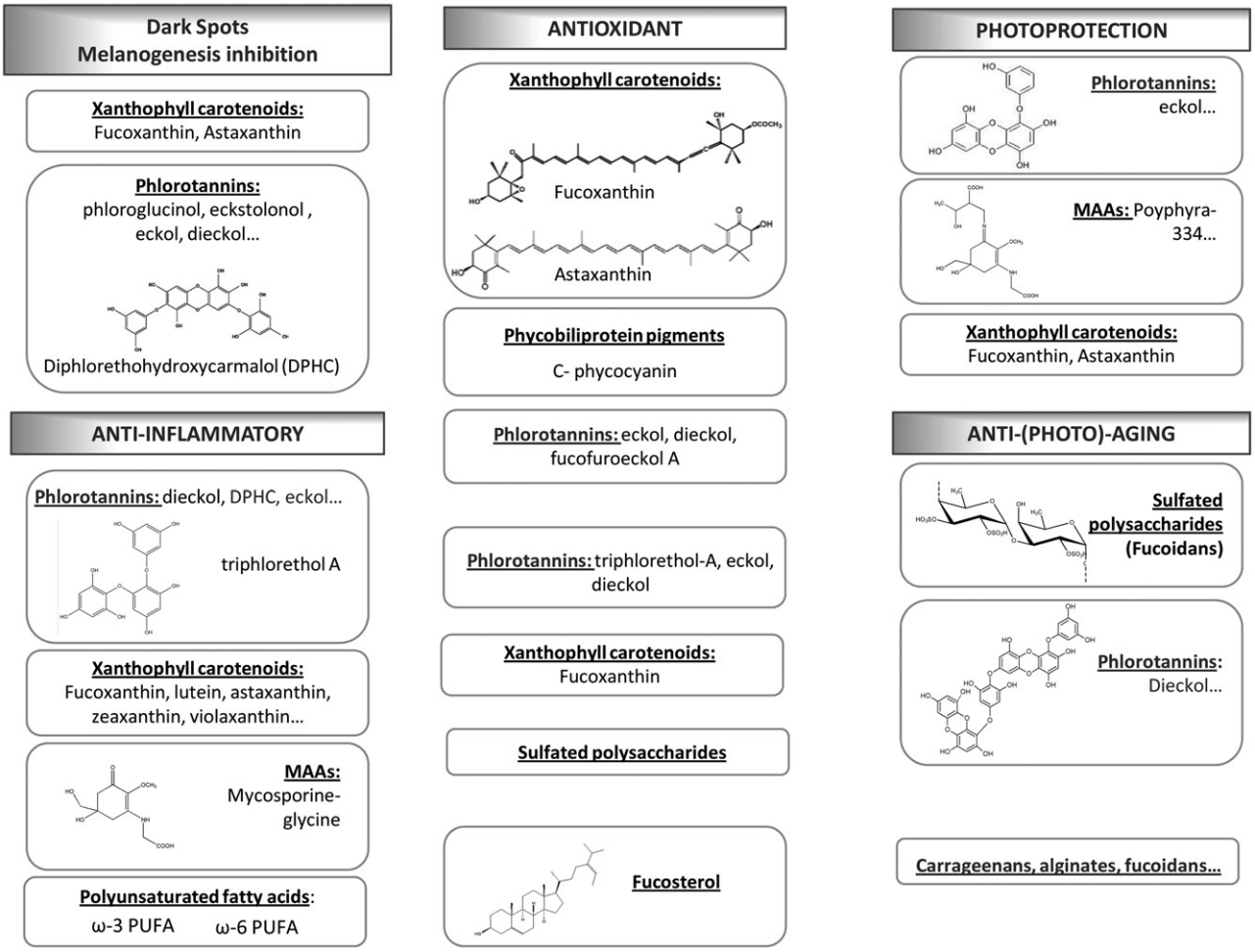

Figure 3. Examples of bioactive compounds extracted from algae. Bioactive metabolites produced from algae give numerous opportunities to be used as active ingredients. Additionally, they offer multiple cosmetic benefits.

microalgae such as *Porphyridium cruentum*), and (ii) contributing to the anti-inflammation that may be attributed to the down-regulation of NF-κB in nucleus and the inhibition of proinflammatory modulators including IL-1β, IL-6, TNF-α, and COX-2 [29].

Heterofucans (sulphated polysaccharides) from *Decidua menstrualis* decrease inflammation by directly binding to the cell surface of leukocytes, especially polymorphonuclear cells (PMNs).

Yu and Gu [30] suggested that PS can also form a protective membrane to prevent water evaporation in skin.

Fucoidan (sulphated polysaccharides) from brown algae, act on the migration and proliferation of fibroblasts and modulate connective tissue proteolysis. Thomas and Kim [31] noted that *in vitro* it can inhibit UVB-induced MMP-1 expression by the suppression of extracellular signal regulated kinase, and suppress MMP-3 induction on dermal fibroblasts. Fucoidan obtained from *Costania costata* is active against UVB-induced MMP-1 promoter, mRNA, and protein expression in human keratinocyte cells *in vitro*. In addition, *ex vivo* results showed that fucoidan can minimise human leukocyte elastase activity, resulting in protection of the skin's elastic fibre network against enzymatic proteolysis [6]. Fucoidan in the presence of transforming growth factor-β (TGF-β) has been reported to enhance healing by increasing fibroblast repopulation. It seems that the risk of inflammatory pathologies involving extracellular matrix degradation by MMPS could be reduced by seaweed fucoidans.

Sulfated PS from the red microalgae *Porphyridium* appear to be an excellent candidate to substitute hyaluronic acid as a biolubricant and exhibited antioxidant activity against the auto-oxidation of linoleic acid [32]. It is also known that sulphated PS from green seaweeds exert an antioxidant action by scavenging free-radicals (superoxide, hydroxyl, 1,1-diphenyl-2-picrylhydrazyl (DPPH)-radicals) [33].

Laminarin, alginate, and fucoidan derived from brown algae (*Turbinaria conoides*) also have antioxidative properties, and can be applied to prevent skin

Table 1. Example of marine sources containing bioactive compounds, which can be used in cosmetic applications.

Bioactive compounds	Source	Biological actions	References
Mycosporine-like amino acids (MAA)			
Aminocyclohexenone-type	Red algae:	Antioxidant	[37,40]
Aminocyclohexene imine-type	*Porphyra* sp.	Antiinflammatory	
	Catenella repens	Photoprotection (absorbs UV irradiation)	
	Green algae:	Antiaging	
	Chlamydomonas hedleyi		
	Brown algae:		
	Padina crassa,		
	Desmarestia aculeatia		
Sulphated (exo)-polysacharide:			
Fucoidans	Red algae:	Antioxidant	[53]
Fucans	*Porphyridium* sp.	Antiinflammatory	
Highly sulphated galactan	Brown algae:	Antiaging	
	Costaria costata		
	Green algae:		
	Ulva lactuca		
	Diatoms:		
	Cylindrotheca closterium		
β-type heteropolysaccharide	*Isochrysis galbana*	Antioxidant	[54]
Phycobiliprotein pigments			
R-phycoerythrin	Red algae:	Antioxidant	[55]
Phycocyanin	*Gracilaria gracilis*	Anti-melanogenic (whitening)	
Allophycocyanin	Blue-green algae:		
	Spirulina platensis		
	Red algae:		
	Porphyridium sp.		
Xanthophyll carotenoids (lipid-soluble pigments)			
β-carotene	Green algae:	Antioxidant	[56]
	Dunaliella salina	Antiinflammatory	
	Haematococcus sp.	Anti-photoaging	
Lutein	Green algae:	Antioxidant	[56]
	Dunaliella salina,	Antiinflammatory	
	Chlorella sorokiniana	Photoprotection/	
		Anti-photoaging	
Zeaxanthin	Blue-green algae:	Antioxidant	
	Synechocystis sp.	Antiinflammatory	
	Green algae:		
	Chlorella saccharophila		
Zeaxanthin	Red algae:	Antioxidant	[57]
α- and β-carotene	*Porphyra* sp.	Anti-inflammatory	
Lutein		Photoprotection/	
Anteraxanthin		anti-photoaging	
β-carotene,	Green algae:	Antioxidant	[61]
Zeaxanthin	*Dunaliella salina*	Antiinflammatory	
Neoxanthin	*Ulva lactuca*	Photoprotection	
Anteraxanthin		Anti-photoaging	
Violaxanthins			
Siphonein			
Siphonaxanthin			
Asthaxanthin	Green algae	Antioxidant	[58]
	Haematococcus pluvialis	Antiinflammatory	
	Chlorella zofigiensis	Photoprotection/	
	Chlorococcum sp.	Anti-photoaging	
		Anti-melanogenic (whitening)	
Fucoxanthin	Brown algae:	Antioxidant (via Nrf2 signalling),	[59]
	Sargasum siliquastrum	antiinflammatory,	
	Diatoms:	Anti-melanogenic (whitening)	
	Chaetoceros sp.		
	Odontella aurita		
Lipids			
Eicosapentaeonic (EPA), Docosahexaeonic (DHA)	Green algae:	Antioxidant	[55]
Eicosatetraenoic acid (ETA) Polyunsaturated ω-3 fatty acids	*Tetraselmis* sp.	Antiinflammatory	
	Nannochloropsis sp.	Anti-photoaging	
	Red algae:		
	Porphyridium sp.		
	Cyanobacteria:		
	Spirinula plantensis		
Glycolipids			
Monogalactosyldiacylglyceride Digalactosyldiacylglyceride	Diatom:	Antioxidant	[60]
Sulfoquinovosyl diacylglycerol	*Stephanodiscus* sp.	Antiinflammatory	
Phlorotannins			
Fucophloroethol, Fucodiphloroethol	Brown algae:	Antioxidant	[61]
Fucotriphloroethol	*Fucus vesiculosus*	Antiinflammatory	
Phlorofucofuroeckol bieckol/dieckol	*Cystoseira nodicaulis*	Anti-melanogenic (whitening)	
	Cystoseira tamariscifolia	Anti-histaminic	
	Cystoseira usneoides	Antiaging	
	Ecklonia cava	Photoprotection	

aging. It should be noted that alginate acts as a thickening and water-binding agent.

Low molecular weight polysaccharides, (≤10 kDa) obtained from *Pyropia yezoensis* (red algae), have numerous biological functions, including antioxidant, antitumor, antifatigue, and anti-inflammatory activities, and have been shown to protect against UVA-induced photoaging [34]. Recently, Kim et al. [35] examined the *P. yezoensis* peptide, PYP1-5, for its antiaging function by promoting collagen synthesis in human dermal fibroblasts. Their results indicate that PYP1-5 promotes collagen synthesis. Moreover, these authors suggested that PYP1-5 promotes the synthesis of other ECM products (such as elastin), and suppresses the MMP-1 protein and mRNA expression levels, enhanced the TIMP-1 and -2 protein and their mRNA expression levels. It also appears that PYP1-5 upregulated the TGF-β1 protein and mRNA levels in a dose-dependent manner, TGF-β being the major activator of the collagen synthesis process in skin fibroblasts. Finally, PYP1-5 activates the TGF-β/Smad signalling pathway, which subsequently induces collagen synthesis.

Thus, the polysaccharides from marine algae have interesting properties and potentialities for cosmetic functions, even if their use needs to be further explored.

MAAs

MAAs are natural compounds found in a wide variety of organisms, including cyanobacteria and macroalgae. Owing to the positive effects on cell regeneration observed in human skin fibroblasts, MAAs seem to be potential cosmetic agents. They are low molecular weight water-soluble molecules and this family consists of ∼30 members, including mycosporine-glycine (M-Gly), palythine, palythinol, asterina-330, porphyra-334, and shinorine, the latter being the most abundant MAA in many microalgae species. They are identified in all the major divisions of marine algae, and possess significant chemoprotective effects against photoinduced skin aging. They are involved in DNA repair systems, radical quenching and have antioxidants properties.

They received much attention for their functional roles in UV photoprotection and ROS scavenging as they have been shown to decrease the direct and indirect damaging effects of environmental UVR. This capacity to prevent UV-induced damage has been reported *in vivo* and *in vitro* studies [36]. M-Gly protects cells from UV-induced cell death, and treatment with M-Gly results in a significant decrease in UV-induced COX-2 mRNA levels, showing also anti-inflammatory properties of MAAs. Porphyra-334 and shinorine from *Chlamydomonas hedleyi* (a green microalgae) act as antiaging factors by modulating the expression of genes associated with aging in the skin, such as procollagen C proteinase enhancer (PCOLCE) and elastin, PCOLCE being an important determinate of procollagen playing a role in the regulation of collagen deposition in the skin [37].

Recently, Ruy et al. [38] showed that porphyra-334 from *P. yezoensis* suppress ROS production and the expression of MMPs following UVA irradiation, while increasing levels of ECM components (procollagen, type 1 collagen, and elastin). MAAs from microalgae such as *Spirulina*, *Chlorella* and *Dunaliella* are also known to reduce UV-induced damage. In addition, MAAs are also involved in the modulation of skin fibroblasts proliferation. Besides, it has been suggested that MAAs also have a role in osmotic regulation, particularly in cyanobacterial communities. Thus, MAAs from algae have antiphotoaging activities and can inspire applications as skin care products.

Pigments and phenolic compounds

Algae contain different types of pigments, which are specific to particular groups: the green, brown, red, and blue-green algae. Scytonemin is a yellow-brown lipid soluble pigment located in the extracellular polysaccharide sheath of some cyanobacteria, and is redox sensitive. This pigment may be effective in shielding the cells from incoming near-UV and blue radiation, but not from green or red light. However, the basis for its biological activity is not well understood [39].

Carotenoids are natural isoprenoid pigments biosynthesized by all photosynthetic plants, protists, and bacteria, as well as some heterotrophic bacteria, some fungi, and some invertebrates. They are important natural lipid-soluble pigments that directly provide photoprotection against UV light-induced photooxidation in the skin. Marine microalgae contain up to 0.2% of carotenoids. They are powerful antioxidants thanks to their ability to quench singlet oxygen, to be oxidised and to be isomerised. The main sources of carotenoids are microalgae that belong to the Chlorophyceae family. *Dunaliella* has the highest content of β-carotene, and *Haematococcus pluvialis* accumulates the highest levels of xanthophylls (astaxanthin). Microalgae synthesise all xanthophylls produced by higher plants (violaxanthin, anteraxanthin, zeaxanthin, neoxanthin, and lutein), and they can also produce others, such as astaxanthin, loroxanthin, and caraxanthin. Fucoxanthin, diatoxanthin, and diadinoxanthin are produced by brown algae or diatoms.

β-carotene is known to modulate UVA-induced gene expression in human keratinocytes. Their anti-inflammatory activity is related to modulation of various biological targets including NF-κB, COX-2, and MMP-9.

Astaxanthin (Figure 3), a red carotenoid pigment, displays antioxidant properties stronger than vitamin E and β-carotene. As an antioxidant, it scavenges free radicals and protects the lipid bilayer from peroxidation and inhibits H_2O_2-mediated activation of the transcription factor NF-κB. Subsequently, astaxanthin blocks proinflammatory cytokine production [41]. *In vitro* studies and topical application of a liposomal formulation containing astaxanthin demonstrated protective effects against UV-induced skin cell death and damage [42,43]. Astaxanthin derived from *Haematococcus pluvialis* (green algae) shows improvements in skin wrinkle and skin texture, and has an effective protection against photooxidative damage. It should also be noted that *in vitro* protective effect of astaxanthin against UV-induced photooxidation appears to be stronger when compared with lutein and β-carotene [44].

Other natural xanthophyll pigments like violaxanthin isolated from *Chlorella ellipsoidea*, show anti-inflammatory properties by inhibiting NF-κB activation, NO, and PGE_2 production [45].

Fucoxanthin has been found to stimulate the endogenous antioxidant defence through activation of Nrf2/ARE signalling in human keratinocytes [46], one of the major ways by which fucoxanthin treatment eliminates oxidative damage being the Akt/Nrf2/GSH reduced glutathione dependent antioxidant response. *In vitro*, it reduced levels of ROS, inhibited DNA damage, restored mitochondrial membrane potential, and suppressed apoptosis [47]. Moreover, it appears that topical treatment with fucoxanthin significantly reduced UVB-induced epidermal hypertrophy, Vascular Endothelial Growth Factor (VEGF), and MMP-13 expression in the epidermis and lipid peroxidation in the skin. Fucoxanthin obtained from brown algae (*Sargassum saliquastrum*) showed antioxidant activities against hydrogen-peroxide-induced cell damage. Fucoxanthin from *Hijika fusiformis* (brown algae) also showed potent antioxidant activity against 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging.

Fucoxanthin isolated from *Laminaria japonica*, has been reported to suppress tyrosinase activity in UVB-irradiated pigs and melanogenesis in UVB-irradiated mice. The use of tyrosinase inhibitors is the most common method for skin whitening, as the enzyme catalyses the rate-limiting step of pigmentation [31]. It should be noted that other secondary metabolites from brown algae, such as phloroglucinol derivatives, also have tyrosinase inhibitory activity due to their capacity to chelate cooper.

The presence of phenolic antioxidants is less well documented in algae than in terrestrial plants. There are marked differences existing in structures of terrestrial polyphenol compounds compared to marine polyphenols (phlorotannins). Flavonoids and gallic acid are the building blocks of terrestrial polyphenols but phlorotannins (reported only in brown algae) are chains of 1,3,5-trihydroxybenzene formed in the acetate–malonate pathway with a wide range of molecular weights from 126 to 65,000 Da [48]. Algae containing phenolic compounds exhibit many activities such as antioxidant, antiradical, antiallergic, anti-inflammatory, and UV protection functions.

Among phenolic compounds isolated from algae, phlorotannins are one of the most important naturally occurring secondary metabolites with a wide range of functional and bioactive properties. Phlorotannins are composed by oligomers of phloroglucinol (fucols, phlorethols, and eckols). They have demonstrated multiple biological activities such as antioxidant effect, free radical scavenging, anti-inflammatory, and hyaluronidase inhibitory activities (*Eisenia bicyclis*). They are able to chelate metal ions following the presence of hydroxyl groups. They also can inhibit histamine-release observed in skin inflammatory diseases that include atopic dermatitis [49].

As previously mentioned, the aging process reduces the skin thickness, the elasticity, and gives rise to emerging wrinkles. Two major antiwrinkling properties associated with phlorotannins including MMP inhibitory activities and hyaluronidase inhibitory activity, have been investigated. Conventionally used biological models have demonstrated their beneficial effects on antiaging applications such as inhibition of MMP 1, 8 and 13, responsible for the degradation of collagen. Thomas and Kim [31] noted that phlorotannins isolated from *Ecklonia stolonifera*, interfered with the expression of NF-κB that controls the transcription of DNA, and with AP-1, inducing the enhancement of MMP-1 expression. Kim et al. [50] reported that fucosterol treatment on HaCaT, a natural sterol compound isolated from brown algae, decreased UV-irradiated MMPs production and expression, increasing type-1 procollagen production.

The phenolic compound named Sargachromanol E, which is extracted from *Sargassum horneri*, a marine brown algae, suppressed intracellular formation of ROS, membrane protein oxidation, lipid peroxidation, and expression of collagenases such as MMP-1, MMP-2, and MMP-9, all of which are caused by UVA exposure [39]. It was further found that these inhibitions were related to an increase in the expression of the tissue inhibitor of

metalloproteinase (TIMP) genes, TIMP1 and TIMP2. Antiwrinkle properties of phlorotannins have less been investigated. Ferreres et al. [51] reported that six phlorotannins isolated from four brown seaweeds have potent hyaluronidase inhibitory activities. Shibata et al. [52] reported that four phlorotannins namely dieckol, eckol, phloroglucinol, phlorofucofuroeckol A 8,8′-bieckol separated from *E. kurome* and *E. bicyclis* (brown algae) have ability to inhibit hyaluronidase activity, hyaluronidase inhibition being highest compared with three known hyaluronidase inhibitors including catechin, epigallocatechin gallate and disodium cromoglycate.

Thus, phlorotannins have multiple properties that make these highly potential for skin care.

Conclusions

Human skin exposed to solar UV radiation and pollution dramatically increases ROS production and oxidative stress, inducing a cascade of events that involve a variety of cell/molecular signalling pathways. The oxidative stress effects on skin aging induce damage to DNA, reduce production of antioxidants, and activation/inhibition of various signalling factors that ultimately lead to the production of MMPs that degrade collagen and elastin in the dermal skin layer. In adapting themselves to new environments, macro and microalgae produce a wide variety of secondary (biologically active) metabolites which cannot be found in other organisms. Several of them have been studied for their antiaging effects on skin, including antiphotoaging, antifree radical activity, moisturisation, and collagen biosynthesis. In fact, algae are rich sources of biologically active metabolites such as polysaccharides, carotenoids, phlorotannins present in green, red, brown algae, or in microalgae, and represent attractive source to fight against the skin aging process. They have the potential to decrease oxidative stress and increase skin cellular longevity in human skin.

Disclosure statement

No potential conflict of interest was reported by the authors.

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