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Review

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Potential biomedical applications of marine algae

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ABSTRACT

Functional components extracted from algal biomass are widely used as dietary and health supplements with a variety of applications in food science and technology. In contrast, the applications of algae in dermal-related products have received much less attention, despite that algae also possess high potential for the uses in anti-infection, anti-aging, skin-whitening, and skin tumor treatments. This review, therefore, focuses on integrating studies on algae pertinent to human skin care, health and therapy. The active compounds in algae related to human skin treatments are mentioned and the possible mechanisms involved are described. The main purpose of this review is to identify serviceable algae functions in skin treatments to facilitate practical applications in this high-potential area.

Keywords: Algae, dermatology, acne, UV, skin whitening, melanoma

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1. Introduction

1.1. Marine algae

Marine algae, also known as macroalgae or seaweed, are photosynthetic eukaryotic organisms that can be found in coastal areas with tenacious vitality. There are three main macroalgae taxa according to their morphological pigmentations: *Rhodophyta* (red algae), *Chlorophyta* (green algae), and *Phaeophyceae* (brown algae) (Yu et al., 2014). Environmental factors, such as temperature, salinity, sunlight, pH, physiological status and CO_2 supply could influence the chemical composition of marine algae (Trivedi et al., 2015; He et al., 2013a, 2013b). Macroalgae can survive in harsh environmental conditions because of different adaptation strategies. Macroalgae's physiology changes due to the necessary mechanisms of adaption, and as a result, macroalgae produces different secondary metabolites so as to conquer different environments. Macroalgae can even endure extremely high light intensity or very low light intensity in diverse habitats, for example, dessert and arctic region (Pallela et al., 2010). To survive in such various diverse and extreme environments, macroalgae produce a variety of natural bioactive compounds and metabolites, such as polysaccharides, polyunsaturated fatty acids, and phlorotannins (Cheng et al., 2010; Hultberg et al., 2013). Since macroalgae are one of the most commonly studied and used marine resources (Show et al., 2015; Chew et al., 2017), bioactivities of the constituent components of marine algae have been widely investigated. The bioactive compounds such as polyphenols exhibit anticancer, antidiabetic, antioxidant, and anti-inflammatory activities (Fernando et al., 2016). Polysaccharides often show significant antioxidant and immunomodulatory activities. Due to the increasing needs for natural and environmental friendly products, especially in nutraceutical and cosmetics industries, much effort has been made on evaluating the potential of applying bioactive compounds derived from macroalgae on functional foods, cosmeceuticals, and pharmaceuticals. In particular, there are more potential applications of bioactive compounds from macroalgae on dermatology conditions or diseases such as acne, skin aging, pigmentation and

melanoma. Thus, this review is aimed to provide detailed information on how the bioactive compounds derived from macroalgae can be applied to treat the commonly found skin diseases.

1.2. Polysaccharides

Polysaccharides are usually the major component of red, green, and brown algae (Goo et al., 2013; Kurniawati et al., 2014). Various polysaccharides constitute the main composition of the cell walls of algae. The main polysaccharides in algae include agar, alginates, galactans, carrageenans, laminarans, fucoidan and ulvans. Thus, polysaccharides play the role of structural support as well as storage function in algae. In general, algal macromolecules are formed with various monosaccharides linked by glucosidic bonds, and some also have linear backbones containing repeating disaccharide units (Pérez et al., 2016). Alginate, laminarinan, and fucoidan are usually found in brown algae. Alginates are anionic with molecular weight range from 500 to 1,000 kDa, they are made up of α-L-guluronic acid (G) and β-D-mannuronic acid (M) (Vera et al., 2011). Laminarinans and fucoidans are the main water-soluble polysaccharides of brown algae, while laminarinans are the most abundant polysaccharides stored in brown algae. Carrageenan and agar are found in red algae. Carrageenans are the major components of red algae cell walls, and they are linear polysaccharides chains with sulphate half-esters attached to the sugar unit. According to the degree of molecular sulphation, carrageenans are divided into three forms: kappa, lambda, and iota (Vera et al., 2011). Agars are the mixture of linear polysaccharide agarose as well as a heterogeneous mixture of smaller molecules called agaropectin (Williams and Phillips, 2000； Kumar et al., 2013). Ulvan and cellulose are usually from green algae. Ulvan is a kind of water-soluble polysaccharides isolated from green algae, with an average molecular weight ranging from 89 to 8,200 kDa (Alves, et al., 2013).

1.3. Lipids, fatty acids and sterols

Algae lipids consist of glycolipids，phospholipids and non-polar glycerolipids (neutral lipids) (Ansari et al., 2015; López Barreiro et al., 2014; Nakanishi et al., 2014; Soh et al., 2014). Phospholipids are characterized by the presence of a phosphate group at sn-3 position. The main phospholipids derived from algae include phosphatidylglycerol (PG), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI) and phoshatidic acid (PA) (Kumari et al., 2013).

Fatty acids (FA) are carboxylic acids with long aliphatic chains which may be straight or branched, saturated or unsaturated (Mohan et al., 2015). The carbon number of natural FAs is usually even (C4-C28), however, odd chain FAs also exist in algae. According to the number of double bonds, FAs are divided into monounsaturated fatty acids (MUFAs, with one double bond) and polyunsaturated fatty acids (PUFAs, with more than 2 double bonds) (Grama et al., 2014). 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 (Fontana et al., 2007; Ritter et al., 2008).

Sterols are the important structural components of cell membranes which can regulate membrane permeability and fluidity. The basic structure of sterol is composed of four rings (A, B, C, D) and with a hydroxyl group at C3，two methyl groups at C18 and C19, and a side chain at C17. The common sterols found in algae are fucosterol, cholesterol, isofucosterol, and clionasterol (Kumari et al., 2013).

1.4.Phenolic compounds

Phenolic compounds are the secondary metabolites of algae which not directly take part in physiological process such as photosynthesis, reproduction and cell division. They are biosynthesized through the shikimic acid and acetate–malonate pathways (Fernando et al., 2016). Phenolic compounds

are characterized by aromatic ring with hydroxyl groups. Aromatic ring with one or two hydroxyl groups are defined as simple phenols, such as benzoic acids and hydroxycinnamic, and their derivates also have been found in algae (Gupta et al., 2011). Polyphenols are characterized by the presence of a number of phenol units. The characteristic and number of the phenol structural units determine the unique chemical, physical, and biological properties of particular polyphenols class, such as phloroglucinols and phlorptannins. Based on the inter-linkage, phlorotannins can be further subdivided into some groups such as phloroglucinol, eckol and dieckol (Pérez et al., 2016). In recent years, phenolic compounds derived from marine algae have been explored with a broad spectrum of beneficial bioactivity, such as anticancer, antioxidant, antimicrobial, anti-inflammatory activities, and the antioxidant activity. Consequently, more attentions have been paid to their applications on pharmaceuticals, functional foods, nutraceuticals and cosmeceuticals (Fernando et al., 2016).

1.5.Pigments

As photosynthetic organisms, algae can synthesize three kinds of pigments: chlorophylls, carotenoids and phycobiliproteins (Pérez et al., 2016). The pigments in algae determines the color of algae. 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 (Pérez et al., 2016). The pigments in brown algae are usually chlorophylls a, c1, and c2, β-carotene, and fucoxanthin (Sharma 2011).

Except for the compounds listed above, there are certain other compounds in seaweeds, such as lectins, alkaloids, terpenes, and halogenated compounds. These bioactive compounds isolated from marine algae have been reported with antibacterial, anti-inflammatory, antioxidant, anti-tumor activity, and thus have great prospects in the food, pharmaceutical, cosmeceutical, and nutraceutical industries (Jin et al., 2014). Here we will focus on the potential applications of marine algae on dermatology symptoms including UV protection, skin whitening and melanoma treatments.

1.6.Human skin

Human skin is the largest organ of the integumentary system which covers the whole body surface (Wang et al., 2015). Skin is a complex organ consisting of three primary layers: the epidermis, the dermis and the hypodermis. The epidermis is the outmost layer of skin, which plays a role of protection from environmental damage and is waterproof. The epidermis has no blood vessels, and the main cells contain keratinocytes (content about 95%), melanocytes, Merkel cells, and Langerhans cells. The epidermis could be subdivided into three cellular strata, the uppermost is a horny surface layer, which are composed of flattened cells containing the tough, proteinaceous substance keratin (Wu et al., 2015). The horny layer plays a photo protective role by reflecting solar radiation. Beneath the horny layer is a layer of flattened cells containing granules of eleidin, the precursor of keratin. Finally, the granular layer, is the bottom most basal layer.

Since skin directly interacts with environment, it is sensitive to stimulus and even damage from chemical and physical substances, especially, from ultraviolet (UV) radiation (Ma et al., 2014). UV radiation, includes UV-A, UV-B and UV-C. UV-A radiation is long–wavelength Ultraviolet (wavelength: 315~400 nm). It can go through clouds, window glass and reach the dermis. Tanning of skin on exposure, wrinkles and skin cancer are all caused by UV-A radiation. UV-A radiation can be classified into two types. UV-A-1 (340~400 nm) is the most powerful UV radiation, also the most harmful one. It is main reason that leads to human skin ageing, wrinkles and pigmentation (Wang et al., 2011). On the other hand, UV-A-2 (320~340 nm) causes sunburn and actinic keratosis. Because UV-A radiation can always penetrate the atmosphere, it will accumulate over a period of time in skin and let skin become older. UV-B radiation is middle–wavelength Ultraviolet (280~315 nm). Most of it can be absorbed by ozonosphere, but the neglected UVB (and UV-A-2) radiation will reach the epidermis. UV-B radiation causes erythema, swelling, hot or painful lesions in skin, even result blisters or peeling. UV-B radiation is at its strongest at noon to mid-afternoon, around 12 to 4 pm. UV-C radiation is

short–wavelength Ultraviolet (100~280 nm). Almost none of UV-C can penetrate Ozonosphere, so it causes less damage than UV-A and UV-B radiation. Continuous exposure to UV irradiation usually leads to a lot of complication, such as sunburn, hypopigmentation and even skin cancer (Zhong et al., 2015).

The color of human skin is determined by melanin, a polymeric pigment manufactured by special dendritic cells known as melanocytes. Melanocytes are cells in the basal membrane of the epidermis with a content between 5% and 10%. Melanocytes are vividly described as unicellular "glands" due to their long, thin, branching, and streamer-like dendrites. The dendrites worm their way between the epidermal cells. As a result, a melanocyte is surrounded by a series of epidermal cells. Melanin is produced in the melanosomes (small vesicals budding from melanocytes' Golgi apparatus). Once produced, it is transported to the dendrites of the melanocyte (Chen et al., 2015). Epidermal cells contact with the melanin laden dendrites and phagocytose the tips of dendrites, finally transfer the melanin to surrounding epidermal cells. Once get into the epidermal cells, melanin granules tend to move above the cell nucleus, forming a shroud over it to protect the DNA mutation caused by environmental factors, especially UV radiation (Lugassy et al., 2007; Hseu et al., 2015). Melanin is a polymeric material with several chemical forms, the color of melanin depending on its degree of oxidation. Eumelanins and phaeomelanins are the most commonly melanin found in human skin sometimes also found in hair. They are both derived from L-dopa, experiencing a series of biological oxidative process. Tyrosinase is the most important enzyme in melanin synthesis. It catalyzes two distinct actions: the hydroxylation of L-tyrosine to L-dopa and the oxidation of L-dopa to dopaquinone (Chen et al., 2015). Tyrosinase will be highly activated when exposed to excess UV radiation. Thus, the basic strategies of inhibiting pigmentation are decreasing UV radiation and inhibiting the activity of tyrosinase.

2. Algae against acne vulgaris

Acne vulgaris, known as acne, is a common skin disease or condition affecting many adolescents and young adults. It is characterized by blackheads or whiteheads, pimples, greasy skin, and possible scarring. Acne can persist for years and result in permanent scars, disfigurement and has adverse effects on physiological development (Leyden et al., 1995). The pathogenesis of acne is complex and multifactorial. Generally, it is viewed as an inflammatory disease, other factors such as hair follicle keratinization, sebum secretion, and bacteria can also contribute to acne (Farrar et al., 2004). *Staphylococcus epidermidis, S. aureus,* and *Pseudomonas aeruginosa*, and *S. aureus* are usually involved in acne formation (Yamaguchi et al., 2009). In particular, the gram-positive anaerobic bacteria, *P. acnes*, is often recognized in acne vulgaris. Acne vulgaris due to the growth of bacteria is traditionally treated with antibiotic therapies such as clindamycin and erythromycin. However, extensive application of antibiotics has led to bacterial resistance. Besides, antibiotics may cause skin allergies and skin irritation. Consequently, the bioactive compounds extracted from marine algae could be a safe, natural alternative. Macroalgae extracts have been reported to possess antibacterial and antifungal activities (Pérez et al., 2016). Extracts of various marine algae were examined for their antibacterial activity against skin bacteria and some effective antibacterial compounds were found as summarized in **Table 1**. In addition, extracts from some macroalgae exhibit anti-inflammatory effects and are able to modulate the levels of growth factors and collagen (Lee et al., 2009), which could improve the acne skin condition and speed up skin repair.

Ruxton and Jenkins (2013) found a novel seaweed oligosaccharide-zinc complex (SOZC) from the polysaccharide membrane of Laminaria digitata through a series of double-blind, placebo-controlled, randomized clinical trial (RCT). The findings suggest that SOZC can relieve symptoms of acne, and particularly reducing sebum production and populations of *P. acnes*. Capitanio et al. (2012) investigated whether the complex of seaweed-derived oligosaccharide and zinc could lead to a

significant improvement in mild acne. They found that the seaweed-derived oligosaccharide complexed with 0.1% zinc pyrrolidone resulted in a significant reduction in acne. The antibacterial activity of extracts from seaweeds is solvent dependent. Choi et al. (2011) evaluated the antibacterial activity of methanol and aqueous extracts of seaweed *Eckloniac cava* by disk diffusion method, the inhibition zone of methanol extracts (5 mg $disk^{-1}$) was 5.3 ± 0.3 mm, while aqueous extracts (5 mg $disk^{-1}$) was 2.8 ± 1.0 mm. The commonly used solvents usually include water, ethanol, methanol, ethyl acetate, dichloromethane, acetone, diethyl ether, chloroform and hexane (Pérez et al., 2016).

Some compounds extracted from seaweeds can also reverse the erythromycin and lincomycin resistance of *P. acnes*. For example, Lee et al. (2014) evaluated the methanolic extract of brown seaweed *Eisenia bicyclis* named fucofuroeckol-A (FF) for antibacterial activity against acne-related bacteria. FF exhibited high antibacterial activity with a minimum inhibitory concentration (MIC) ranging from 32 to 128 g mL^{-1}. Moreover, the MIC values of erythromycin-resistant *P. acnes* were reduced from 2,048 to 1.0 g mL^{-1} when in combination with MIC of FF (64 g mL^{-1}), showing a synergistic effect. Amiguet et al. (2011) found the ethyl acetate extract from *Fucus evanescens* exhibited strong antibacterial activity against *P. acnes,* and also against methicillin-resistant *S. aureus.*

3. Algae protects skin from UV radiation injury

Photoaging caused by excess exposure to sunlight became hugely problematic in recent years. As indicated in **Figure 1**, the mechanism is that UV stimulates the formation of reactive oxygen species (ROS) (Pallela et al., 2010), which plays a critical role in cell signaling and homeostasis. However, when skin is exposed to adverse conditions, for instance, UV irradiation or high temperature, the concentration of ROS will arise quickly, and high concentration of ROS may cause damage of cell structure. To keep skin elastic and smooth, the collagen and elastin in dermis play important roles in supporting the epidermis. When exposed to UV irradiation, ROS proliferates quickly, and neutrophils will be activated by high concentrations of ROS (**Figure 1a**). Then ROS causes elastic fibers dystrophy,

and the activated neutrophils secrete neutrophil elastases which activate matrix metalloproteinases (MMPs) (**Figure 1b**) (Chen et al., 2012; Chen et al., 2013). Elastases also cause the degradation of elastic fiber, and MMPs cause the degradation of collagen. When under too much UV radiation, the skin will lose its support and forms wrinkles. Thus, accumulation of MMPs is harmful for skin (**Figure 1c**). Marine organisms, especially macroalgae, produce varieties of prominent photo-protective and anti-photoaging compounds to confront photoaging (Pallela et al., 2010). Bioactive compounds from macroalgae can absorb UV-A and UV-B, and some of them can scavenge the arisen ROS, and inhibit the formation of MMPs.

Several extracts from different algae exhibit photo-protective functions. The compounds in those extracts that have confirmed with the photo-protective activity include shinorine, porphyra-334, palythene, eckstolonol, eckol, mycosporine-glycine, mycosporine methylamine-serine, sargachromenol, fucoxanthin, tetraprenyltoluquinol chromane meroterpenoid, scytonemin, and sargaquinoic acid (Daniel et al., 2004; Urikura et al., 2011; Janga et al., 2012; Kim et al., 2013; Ryu et al., 2014; Balboa et al., 2015). The most efficient UV-A-absorbing compounds in nature are the mycosporine-like amino acids (MAAs) which are water-soluble substances found in plenty of organisms, like cyanobacteria, algae, corals and many marine invertebrates. Porphyra-334, one of MMAs, is refined from the red algae *Porphyraumbilicalis.* Its absorption coefficient at 334 nm is 42,300, showing that its filter capability is similar to those synthetic UV-A sunscreens such as butyl methoxydibenzoylmethane (40,000) (Daniel et al., 2004). Porphyra-334 can decrease intracellular UVA-activated ROS concentration in HDFs based on a modified DCF-DA fluorescence assay. Porphyra-334 controls the expression of MMPs by scavenging the overdose ROS in damaged HDFs (Ryu et al., 2014).

Tetraprenyltoluquinol chromane meroterpenoid (TPM), isolated from *Sargassum muticum*, can protect HDFs from ROS damage. Using oxidant sensitive fluorescent probes (DCFH-DA) to detect intracellular ROS scavenging properties, it was found that TPM reduced 20.6% (for 20 μg mL^{-1}) as

shown by DCF-DA staining, due to the inhibition of intracellular accumulation of ROS in HDFs when exposed to UV-A irradiation. Compared to retinoic acid (for 0.3 μg mL^{-1}) reduced DCF-DA staining as 9.1%, TPM has a better performance. TPM shows its strong anti-photooxidative stress via DCFH-DA (Balboa et al., 2015).

There are also other algae extracts being used to treat photoaging arising from UV-B radiation. Eckstolonol isolated from *Ecklonia cava* was found to protect HaCaT cells from photo-oxidative stress. Jang et al. (2012) tested the antioxidative effects of eckstolonol by using fluorometry, flow cytometry, microscopy, cell viability and comet assays. They found that UV-B-induced ROS of HaCaT cells was obviously decreased, while the viability of eckstolonol-treated cells increased when an eckstolonol concentration of 200 μM was used. The way eckstolonol repairs the UV-B-caused injury is thought due to the increase in the activities of two kinds of antioxidant enzymes, catalase (CAT) and superoxide dismutase (SOD), which can remove the increased ROS, so that the UV-caused damage would be mitigated.

Kim et al. (2013) investigated the anti-photoaging effects and explored the molecular mechanisms of fucosterol in UV-irradiated immortalized HaCaT cells. By using classic methods including ELISA, semi-quantitative reverse transcription-polymerase chain reaction (semi-quantitative RT-PCR), western blot and 2',7'-dichlorofluorescein diacetate assay, it reveals that fucosterol can reduce the concentration of UV-induced MMPs and inflammation caused by cytokine expression through inhibition of mitogen-activated protein kinases (MAPKs) induced by ROS. In addition, fucosterol can also promote Type-I procollagen and anti-oxidant enzyme expression (Kim et al., 2013).

Fucoxanthin is a carotenoid isolated from brown algae. Urikura et al. (2011) used hairless mice to evaluate the anti-photoaging effects of fucoxanthin. Fucoxanthin does not retreat UV-B-damage or protect skin from UV-B radiation, since its UV-B absorption (290–320 nm) is quite weak. However, they found that fucoxanthin is a potent antioxidant because it reduced UV-induced ROS and the

expression of MMP-13. Moreover, Urikura et al. (2011) also reported that fucoxanthin obviously prevents angiogenesis by inhibiting UV-induced VEGF expression in the skin.

4. Algae reduces skin pigmentation

Melanin, is a broad term for a group of natural pigments found in most organisms. In skin, melanogenesis occurs after oxidative stress, especially exposure to ultraviolet (UV) radiation (Lee et al., 2013). Melanin is an effective absorber of light, it is thought to protect the skin cells from damage caused by UV radiation (Tsatmali et al., 2002). Melanin is produced by melanocytes located in the basal epidermal layer. However, if the skin gets enhanced oxidative stress, it causes hyperpigmentation, and it is of most concern. In the first two step of melanin synthesis, tyrosinase acts as the rate-limiting oxidase to catalyze eumelanin and phenomelanin synthesis (Solano et al., 2006). The formation mechanisms of both pigments (eumelanin and phenomelanin) are the same, including tyrosinase catalyzed L-tyrosine hydroxylation to 3, 4-dihydroxy-L-phenylalanine (L-DOPA) and then L-DOPA oxidation to dopaquinone (Parvez et al., 2006). Therefore, tyrosinase inhibitors are thought to be an important and effective constituent of depigmenting and whitening agents (Liang et al., 2012). However, chemical tyrosinase inhibitor may cause side effects. For example, the pigmented contact dermatitis due to kojic acid (García‐Gavín et al., 2010) and a possible genotoxic effect caused by arbutin (Cheng et al., 2007).

Thus, searching for safe and effective skin whitening agents from marine algae can be beneficial for cosmetic industry. In order to find new anti-browning and whitening agents, scientists screened various marine algae for tyrosinase inhibitors, and have found some potential algae. Cha et al. (2011) investigated 43 indigenous marine algae for their tyrosinase inhibitory activity and found that the extracts from *Endarachne binghamiae*, *Schizymenia dubyi, Ecklonia cava* and *Sargassum silquastrum* exhibited potent tyrosinase inhibitory activity similar to kojic acid. Chan et al. (2011) found that ethanolic extract of *Sargassum polycystum* and its non-polar fraction (i.e., hexane fraction)

showed significant cellular tyrosinase inhibitory activity. Quah et al. (2014) also reported that *Sargassum polycystum* and *Padina tenuis* showed tyrosinase inhibitory effects, and possessed potent cytotoxicity in human epidermal melanocyte and Chang cells, thus can serve as promising cosmetic or pharmacological agents. The tyrosinase inhibitors extracted from marine algae include phlorofucofuroeckol A, eckol, dieckol, diphlorethohydroxycarmalol, dioxynodehydroeckol, fucoxanthin, phloroglucinol (Thomas and Kim, 2013).

Fucoidan is a sulfated polysaccharide derived from brown algae such as mozuku, kombu, bladderwrack, wakame, and hijiki. It is widely used as an ingredient in health care products for its immune boosting properties. Song et al. (2015) found that fucoidan inhibits melanin synthesis by down-regulating melanogenesis associated transcription factor (MITF) and tyrosinase protein expression. This result suggests that fucoidan may be used as a new anti-pigmentation ingredient in medical and cosmetic fields. Fucoxanthin, has been described with antioxidant and anti-angiogenic effects, it also has been reported to suppress tyrosinase activity in UVB-irradiated guinea pig and melanogenesis in UVB-irradiated mice. Moreover, topical and oral administration of fucoxanthin can significantly suppress mRNA expression related to melanogenesis such as tyrosinase-related protein 1 (Tyrp I) (Shimoda et al., 2010).

5. Algae for melanoma treatments

Skin cancer is a very common malignancy tumor. Three are three main types of skin cancers: basal cell carcinoma, squamous cell carcinoma, and melanoma. Basal cell carcinoma and squamous cell carcinoma are classified as non-melanoma skin cancer. Melanoma, derived from melanocytes, is the most aggressive and most common skin cancer. Most melanoma consist of various colors from brown to black, and sometimes with pink, red, or fleshy appearance which is more aggressive, and comes along with itching or bleeding. Both genetic and environment factors are responsible for skin cancer, such as fair skin, exposure to sunlight, and multiple benign naevi (Garbe and Leiter, 2009).

Excess exposure to UV radiation is the most important risk factor for skin cancer. Many experimental animal studies have shown that repeated exposure to UV radiation can cause skin cancer (Chiang et al., 2015; Wang et al., 2015; Cordeiro-Stone et al., 2016). Thus, using of sunscreen and decreasing exposure to UV radiation are effective methods to prevent skin cancer. Other treatments such as surgery, chemotherapy, radiation therapy and targeted therapy are also necessary. The commonly used chemotherapy drugs usually has higher cytotoxicity and side effects, which will be harmful to other body organs, even reduce the quality of life and exacerbate disease condition. For example, in the treatment of CTLA-4 antibody therapy in metastatic melanoma, autoimmune-mediated side effects like colitis, hypophysitis, hepatitis, and iridocyclitis may occur (Kähler et al., 2011). Facial palsy may occur in the vemurafenib-treatment of metastatic melanoma (Klein et al., 2013). Exploring more safe and effective drugs for skin cancer is in urgent need.

Antitumor and cytotoxic compounds have been found from marine algae, such as polysaccharides from *Sargassum fusiforme* with anti-liver cancer activity (Fan et al., 2017). Spatane diterpinoids isolated from brown marine algae *Stoechospermum marginatum* can effectively inhibit malignant melanoma growth (Velatooru et al., 2016). Ascophyllan derived from brown seaweed *Ascophyllum nodosum* exhibits in vivo anti-metastatic activity on B16 melanoma cells (Abu et al., 2015). The anti-melanoma mechanisms of bioactive compounds derived from macroalgae usually rely on activating the caspase cascade such as caspase-3, -6, -9, and reducing the expression of cyclindependent kinase (cdk2, cdk4) and matrix metalloprotease family. **Table 2** summarizes the bioactive compounds found in marine algae with anti-skin cancer activity and their related mechanisms.

Fucoidan, a sulfated polysaccharide isolated from brown algae, has been reported to have biological activities including anti-inflammatory effect (Fitton, 2011), anti-viral (Mori et al., 2012), and anti-tumor activity tested and verified *in vitro* and *in vivo* (Kwak, 2014; Azuma et al., 2012; Takeda et al., 2012). As mentioned in the previous section, fucoidan also have been proved to process immune-

modulating, antioxidant and anti-pigmentation activities. Thus, fucoidan may have a wider scope to be explored and applied in pharmaceutical and cosmetic field.

6. Other bioactivities from algae with functions for skin health treatment

In recent years, the antioxidant activity of marine algae has been highly focused by scientists. Compounds with antioxidative properties have been isolated from marine algae (Balboa et al., 2013). The most promising compounds are polysaccharides, phlorotannins and terpenoids. For example, Rupérez et al. (2002) found the potential antioxidant capacity of sulfated polysaccharides from the edible brown seaweed *Fucus vesiculosu.* Phlorotannins, isolated from marine algae such as *E. cava* and *I. okamurae*, exert great antioxidant activity and radio-protective effect through the inhibition of apoptosis via the scavenging of ROS, including decreased levels of pro-apoptotic Bax, p53, caspase-3 and -9, and increased levels of anti-apoptotic Bcl-2 and cytoprotective HO-1 (Shin et al., 2014).

Some seaweeds also have anti-inflammatory effect. By testing the inhibitory effect on NO production, Choi et al. (2011) found the potential anti-inflammatory effect of *E. cava, E. kurome*, and *I. sinicola* extracts. Khan et al (2007) also isolated two anti-inflammatory polyunsaturated fatty acids (PUFAs) and eicosapentaenoic acid (EPA) from brown seaweed *Undaria pinnatifida*. Alma et al. (2016) found a high anti-inflammatory effect of clobetasol propionate in combination therapy with algal oil (containing ω-3 fatty acids).

Alginates, found in *L. digitata*, were observed to promote wound healing, by modulating the levels of growth factors and collagen (Lee et al., 2009). *Pyropia yezoensis* peptide also showed the ability of promoting collagen synthesis by activating the TGF-β/Smad signal pathway (Kim et al., 2017). The aqueous extract of *Spirulina platensis* also showed wound healing activity, and as analyzed by LC-MS/MS, the compounds supposedly involved in accelerating wound healing include cinnamic acid, narigenin, kaempferol, temsirolimus, phosphatidylserine isomeric derivatives and sulphoquinovosyl diacylglycerol (Syarina et al., 2015). Thus, extracts from marine algae might be

considered as a potential source of therapeutic agents for chronic wound healing and associated complications.

7. Future protect and challenges

Marine algae have been confirmed to be rich in potential bioactive compounds such as polysaccharides, carotenoid, sterol, phlorotannins, fatty acids, as well as minerals and vitamins. With the immune-adjusting and disease-defending activity, algae have been long used in food diets and nutritional remedies. Recently, the potential of marine algae used as an ingredient in pharmaceutical and cosmeceutical industries have attracted great attention. In particular, the application of marine algae in dermatology treatment is of huge potential due to their properties of anti-acne, antioxidant, anti-aging, anti-inflammatory, melanogenesis inhibition, UV photo protective and anti-melanoma effects. Scientists have shown that marine algae derived compounds exhibit various beneficial activities on skin health and care (Wijesekara et al., 2010; Syarina et al., 2015; Shimoda et al., 2010; Ryu et al. 2014). Due to the features of large variety, fast growing and being cultivated in seawater, using marine algae has obvious advantages as a source for bioactive products (Barlow et al., 2016; Sarkar et al., 2015; Show et al., 2013; Wang et al., 2016), when compared to terrestrial plants, which also contain bioactive components, in terms of productivity, diversity, and the saving of valuable freshwater resources. Entry into pharmaceutical and cosmeceutical markets, the algae-based bioactivities seem to show a prominent future.

However, there are also challenges in application of marine algal bioactive compounds. Firstly, extraction of functional components from algae is usually difficult and energy/cost intensive. To commercialize the algae-based bioactive products, more efficient and cost-effective extraction methods need to be developed. Meanwhile, the level of standardization, efficacy, and traceability of algae derived products are also required (Hafting et al., 2015). Moreover, to achieve higher productivity and high bioactive content, optimization of algae cultivation technology is demanded. Also, conventional

methods for the breeding of high-performance algal strains for bioactives production may not be efficient. It becomes popular to increase the production of bioactive components through genetic transformation (Charrier et al., 2015; Chen et al., 2014). However, due to the lack of information on genomics and gene regulation mechanism of bioactive compounds in algae, there are still major constraints and limitations hindering the development of this type of research (Hafting et al., 2015). Thus, it may require long-term research to achieve major breakthroughs in this area. In addition, to make the algae-based bioactives in dermatology industry mature, the real effects need to be tested by markets.

8. Conclusions

Marine algae are rich sources of bioactive compounds with anti-bacterial, anti-tumor, and anti-oxidative properties. As a result, increasing attentions have been paid regarding application of algae in pharmaceutical, cosmetic, and food industries. This review explores the application of bioactive compounds and metabolites derived from marine algae in dermatology for acne treatment, UV protection, skin whitening and melanoma. A wide range of compounds, such as polysaccharides, carotenoids, and sterols, have been investigated for cosmeceutical preparations. The evidence indicates the high potential of using algal extracts as effective bioactive ingredients in the treatment of skin disorders and for routine skin care.

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Figure legends

Figure 1. The mechanism of photoaging: **(a)** The amount of ROS increased by UV exposure: UVB usually reach the epidermis, while UVA can penetrate the epidermis, and reach the dermis. When skin is exposed to UV radiation, the concentration of ROS will rise due to the skin antioxidant defenses. **(b)** The damage caused by ROS: When expose to UV radiation, ROS proliferates quickly, and neutrophils will be activated by high concentrations of ROS. Then ROS cause elastic fibers dystrophy, and activated-neutrophils secrete neutrophil elastases which activate matrix metalloproteinases (MMPs). **(c)** The damage caused by MMPs: The degradation of collagen is caused by MMPs, and the degradation of elastic fibers is caused by elastases, leading to collagen-support reduce and loss of skin elasticity, finally promote winkle formation and accelerate skin aging.

Table 1. The extracts obtained from marine algae with anti-acne activity.

Compounds	Algae source	Solvent	Bacteria	MIC ($\mu g\ ml^{-1}$)	MBC ($\mu g\ ml^{-1}$)	References
Sargafuran	*Sargassum macrocarpum*	MeOH	*Propionibacterium acnes*	15		Kamei et al., 2009
			Streptococcus pneumoniae	15		
			Streptococcus pyogenes	15		
Eckloniacava		MeOH	*Propionibacterium acnes*	310		Choi et al., 2011
			Staphylococcus epidermidis	2500		
Ecklonia kurome		MeOH	*Propionibacterium acnes*	310		Choi et al., 2011
			Staphylococcus epidermidis	2500		
Ishige		MeOH	*Propionibacterium*	31		Choi et

sinicola		eOH	*m acnes*	0			al., 2011
			Staphylococcus epidermidis	-			
Symphyocladia latiuscula		M eOH	*Propionibacterium m acnes*	0			Choi et al., 2011
			Staphylococcus epidermidis	16 63 0			
Methanolic extract of E. bicyclis	*Eisenia bicyclis*	M eOH	*Propionibacterium m acnes*	10 24	24	10	Lee et al., 2014
			Staphylococcus epidermidis	>1 024	024	>1	
Sargassum polycystum crude extracts - F1	*Sargassum polycystum*	M eOH	*Propionibacterium m acnes*	25 0	0	50	Kok et al., 2016
Sargassum polycystum crude extracts – F2	*Sargassum polycystum*	M eOH	*Propionibacterium m acnes*	50 0	00	20	Kok et al., 2016
β-D-galactosyl O-linked	*Nunavik*	M eOH	*Propionibacterium m acnes*	15			Amiguet et al., 2011

glycolipid
compound

Table 2. The compounds derived from marine algae with anti-cancer activity.

Compounds	Algae source	Experimental model [1]	Mechanism	References
Chloroform extract	*Stypopodium zonale*	HU melanoma C32 cell line	-	Rocha et al., 2007
Fucose-containing sulfated polysaccharide	*Sargassum henslowianum; Fucus vesiculosus*	MU melanoma B16 cells	The activation of caspase-3	Ale et al., 2011
Elatol	*Laurencia microcladia*	MU melanoma B16F10; MU fibroblast L929 cells; HU lung cancer A549 cells ;HU prostate cancer DU145 cells; HU mammary cancer MCF-7 cells; mice bearing B16F10 cells	Reducing the expression of cyclin-D1, cyclin-E, cyclindependent kinase (cdk)2 and cdk4. And a decrease in bcl-xl and an increase in bak, caspase-9 and p53 expression	Campos et al., 2012
Fucoidan	*Saccharina cichorioides, Fucus evanescens, Undaria*	MU epidermal cells JB6 Cl41; HU colon cancer DLD-1 C cells; HU breast	Inhibiting the EGF-induced neoplastic transformation	Vishchuk et al., 2013

	pinnatifida	cancer T-47D cells; and melanoma RPMI-7951 cell lines		
Sulfated polysaccharide ascophyllan	*Ascophyllum nodosum*	MU B16 melanoma cells; Mice bring sarcoma-180 tumor	Reducing the expression of N-cadherin and enhancing the expression of E-cadherin; Inhibiting the expression of matrix metalloprotease-9 (MMP-9) mRNA and the secretion of MMP-9 protein in B16 cells	Abu et al., 2013
Spatane diterpinoid	*Stoechospermum marginatum*	MU B16F10 Melanoma Cells	Inducing intrinsic mitochondrial apoptosis pathway by generating ROS and inactivation of PI3K/Akt pathway, leading to activation of caspase cascade	Velatoru et al., 2015

(1) MU: murine; HU: human

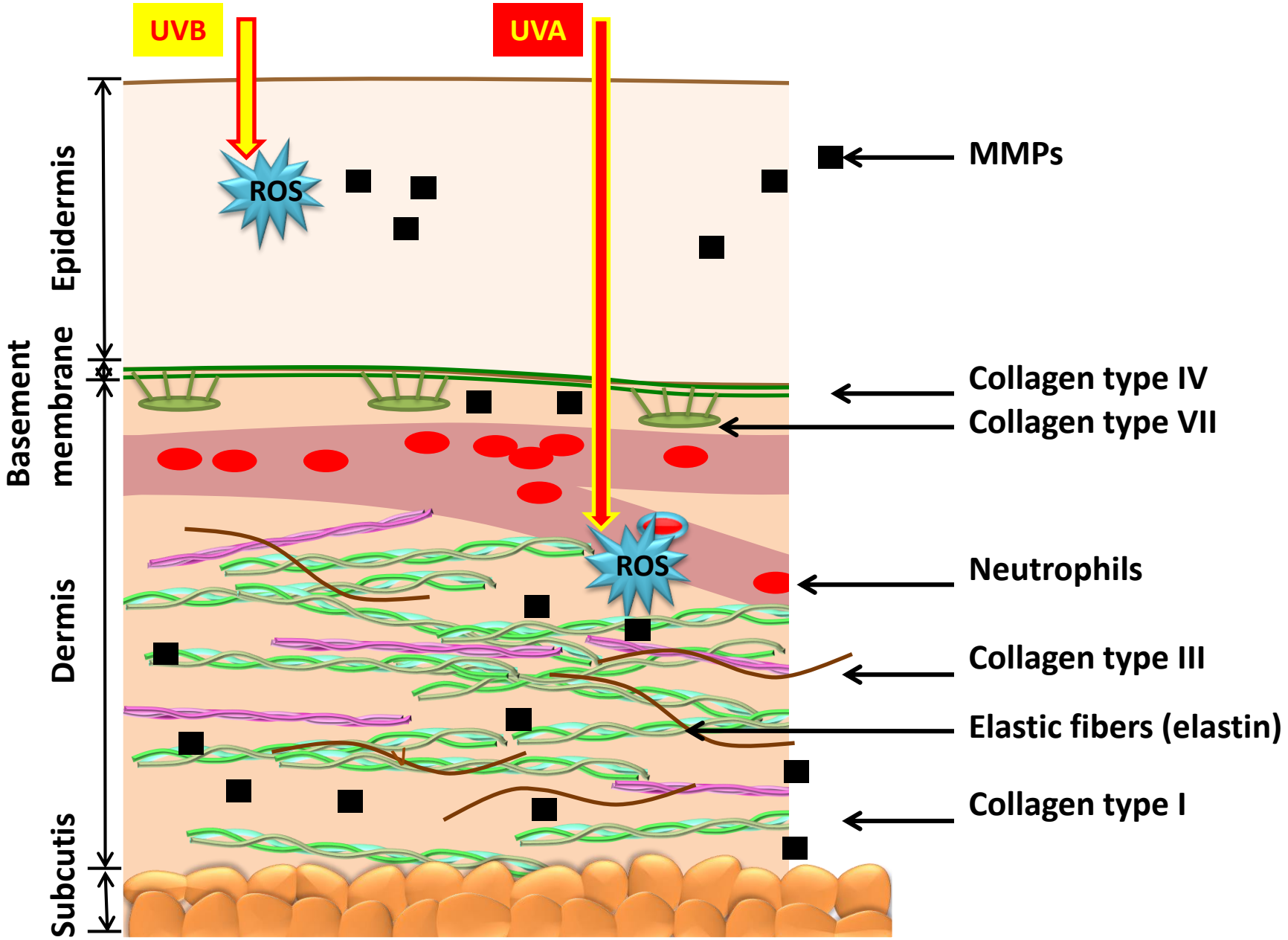
UVB
UVA
ROS
ROS
MMPs
Collagen type IV
Collagen type VII
Neutrophils
Collagen type III
Elastic fibers (elastin)
Collagen type I
Epidermis
Basement membrane
Dermis
Subcutis

Figure 1a

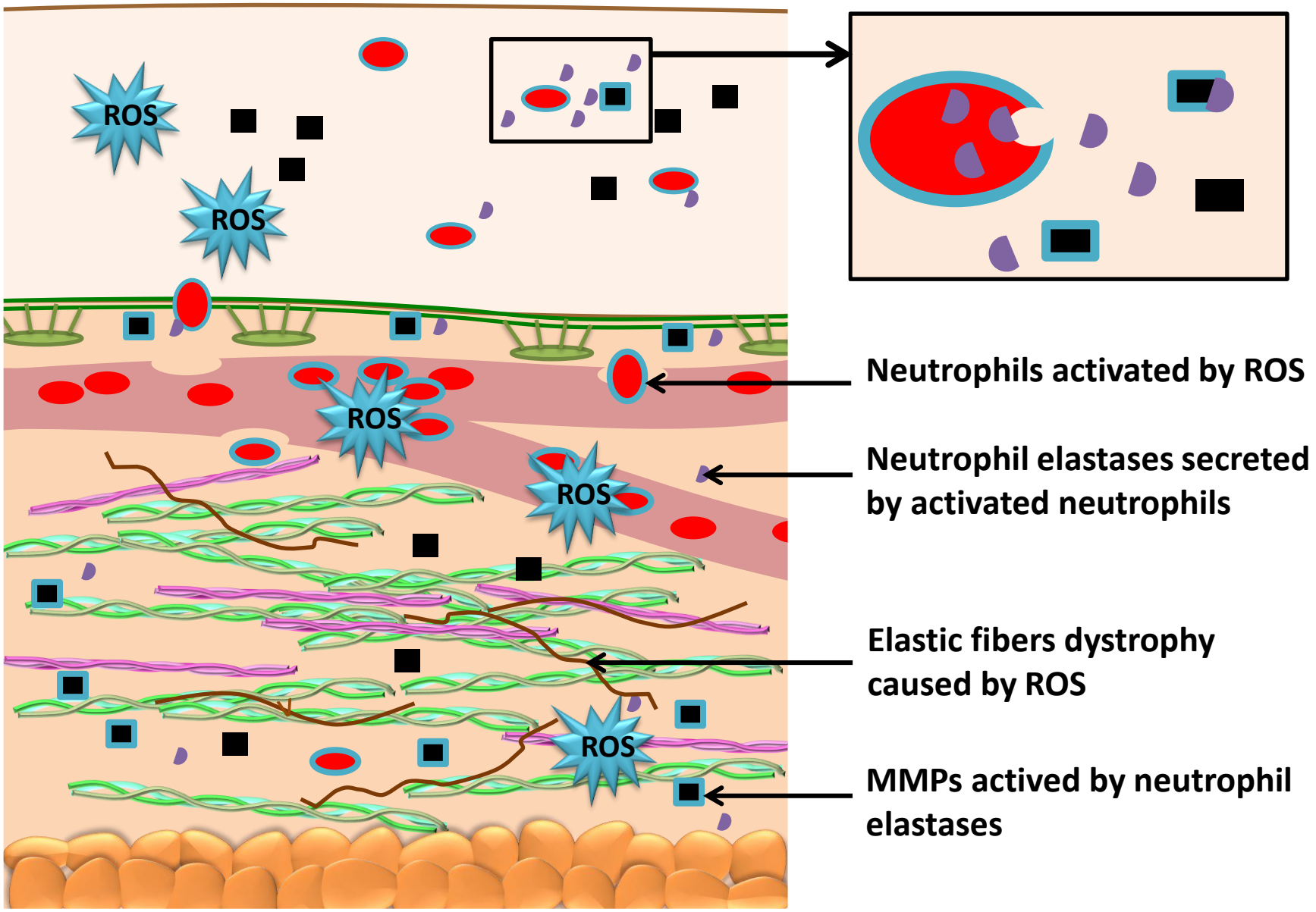
ROS
ROS
ROS
ROS
ROS
Neutrophils activated by ROS
Neutrophil elastases secreted by activated neutrophils
Elastic fibers dystrophy caused by ROS
MMPs actived by neutrophil elastases

Figure 1b

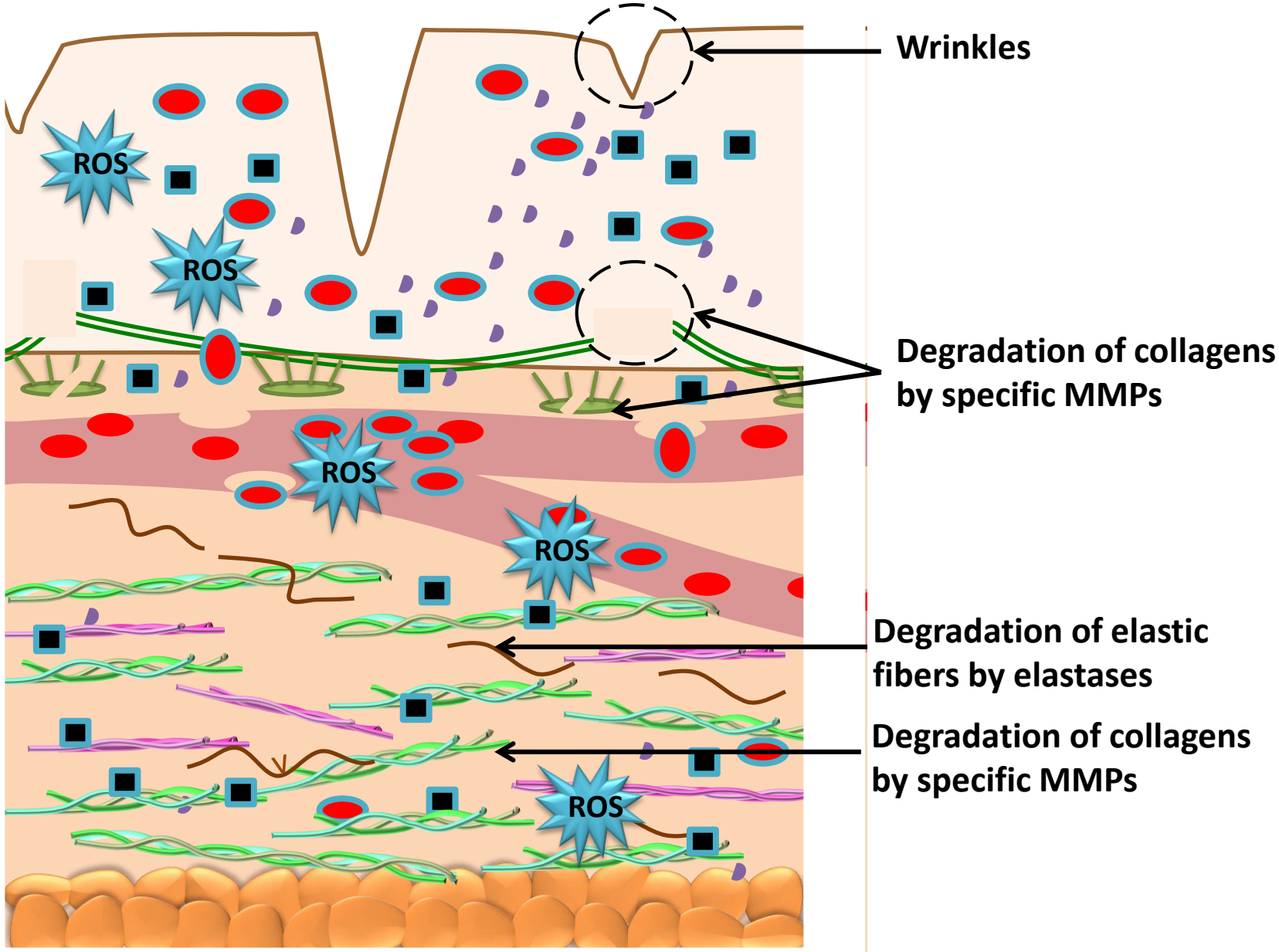
ROS
ROS
ROS
ROS
ROS
Wrinkles
Degradation of collagens by specific MMPs
Degradation of elastic fibers by elastases
Degradation of collagens by specific MMPs

Figure 1c

Highlights

- Marine macroalgae derived compounds are potential therapeutic agents in dermatology
- Seaweed extracts has been shown to protect skin from photo-damage
- Antibacterial compounds derived from macroalgae can fight acne and chronic wounds
- Anti-tumor activity of macroalgae extracts can be exploited to treat melanoma
- Skin whitening and anti-pigmentation properties of seaweed extracts are also discussed