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Review

Beneficial Effects of Marine Algae-Derived Carbohydrates for Skin Health

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Abstract: Marine algae have been considered as abundant source of bioactive compounds with cosmeceutical potential. Recently, a great deal of interest has focused on the health-promoting effects of marine bioactive compounds. Carbohydrate is a major and abundant constitute of marine algae that have been utilized in cosmetic formulations, such as moisturizing and thickening agents. In addition, marine carbohydrates have been suggested as promising bioactive biomaterials for various skin beneficial properties, such as anti-oxidant, anti-melanogenic and anti-skin aging. Therefore, marine algae carbohydrates have potential of skin health benefits for value-added cosmeceutical application. The present review focused on the various biological capacities and potential skin health benefits of bioactive marine carbohydrates.

Keywords: Marine algae; Carbohydrates; Oligosaccharides; Monosaccharides; Skin health; Cosmeceuticals

1. Introduction

Cosmeceuticals can be defined as cosmetic products with biologically active ingredients purporting to pharmaceutical effects on the skin. Recently, great interest has been shown by consumers in novel bioactive compounds from natural sources, instead of synthetic ingredients, thanks to their perceived beneficial effects [1]. Therefore, there are numerous efforts to develop biologically active ingredients from natural organisms [2]. Most studies have been based on terrestrial sources, however, it has been shown that natural compounds isolated from marine sources show higher biological activity than those isolated from terrestrial sources, and as a result, there is a lot of interest in the studies of ingredients using marine natural sources [3, 4]. In particular, the oceans account for about 70% of the Earth's surface and have biodiversity, it is excellent reservoir for natural products [5]. Among various natural organisms, marine algae, which grow much faster than terrestrial plants, are considered as abundant and essential source of numerous constituents for human skin health benefit [2, 6].

Algae refer to photosynthetic organisms with a complex and controversial taxonomy [7]. To date, more than 20,000 species of algae have been identified and there are two kinds of algae depending on size [6]. Macroalgae (seaweeds) are defined as multicellular marine plants that live in coastal areas with simple structures than terrestrial plants [6]. Marine macroalgae are be classified into three species according to their pigments: *Phaeophyceae* (brown macroalgae, *Chromophyta*), *Chlorophyta* (green macroalgae) and *Rhodophyta* (red macroalgae) [6, 8]. In contrast, microalgae are unicellular or simple multicellular species that have the little size and found in various environments [6, 7].

Marine algae are composed of various substances including carbohydrates, lipids, proteins, amino acids, minerals and flavonoids [9]. Among various ingredients, carbohydrates are the most abundant constituents of marine algae [1, 10, 11]. Based on degrees of polymerization (DPs),

carbohydrates, also called saccharides, exist as various forms of monosaccharide, disaccharide, oligosaccharides and polysaccharide in marine algae [1]. Marine carbohydrates have been utilized in cosmeceutical industries due to their chemical and physical properties [12, 13]. Fucoidans/alginate from brown algae, ulvans from green algae and carrageenans/agar from red algae are used as gelling, thickening and stabilizing agents [2, 6, 12, 14]. In addition, accumulating reports suggested that marine carbohydrates have proven to exhibit a skin beneficial potential [2, 12]. The biological activities of marine carbohydrates have known to be linked with their structure determined by DPs (molecular weight, MW), the presence of sulfate group and type of sugars [15]. Therefore, in this review, we discussed skin health for the cosmetic effects of carbohydrates extracted from marine algae, which are considered as sources of excellent carbohydrates.

2. Bioactive effects and potential health benefits of marine algae

2.1. Biological activities of marine algal extracts

Table 1 shows the beneficial effects of marine algal extracts including macroalgae and microalgae for skin health.

Table 1. Bioactive functions of marine algal extracts

Species	Solvent	Function	Mechanism	Ref
Endarachne binghamiae *Sargassum siliquastrum* *Ecklonia cava*	A	Anti-melanogenesis	*In vitro* (B16F10 cells) Mushroom TYR activity (↓) Melanin content (↓) Cellular TYR activity (-)	[16]
S. siliquastrum *E. cava*			*In vivo* (Zebrafish) Melanin content (↓) TYR activity (↓)	
Ishige okamurae Yendo	A	Anti-melanogenesis	*In vitro* (B16F10 cells) Mushroom TYR activity (↓) Melanin content (↓)	[17]
Sargassum polycystum *Padina tenuis*	E	Anti-melanogenesis	*In vitro* (HEMs) Mushroom TYR activity (↓) *In vivo* (Guinea pigs) Melanin content (↓)	[18]
Schizymenia dubyi	A	Anti-melanogenesis	*In vitro* (B16F10 cells) Mushroom TYR activity (↓) Melanin content (↓)	[16]
Sargassum wightii *Padina gymnospora* *Caulerpa peltata* *Gelidiella acerosa*	M, C, EAc, A	Anti-oxidant	*In vitro* DPPH radical (↓) Ferrous ion chelation	[19]
Fucus vesiculosus (Bladder wrack)	A	Anti-skin aging	*In vivo* (human cheek skin) Thickness (↑) Elasticity (↑)	[20]
Blue Lagoon coccoid *Filamentous*	PBS w/o Mg and Ca (pH 7)	Anti-skin aging Skin barrier function	*In vitro* (HEKs, HDFs) Gene expression of INV, LOR, TGM-1, FLG (↑) UVA-induced expression of MMP-1(↓) type 1 collagen (↑)	[21]
			In vivo (Human skin) UVA-induced expression of	

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			MMP-1 (↓) type 1 collagen (↑) level of TEWL (↓)	
Botryococcus braunii	A	Anti-oxidant	*In vitro* (NIH3T3 cells) ORAC (↑), ROS level (↓) DNA damage (↓)	[22]
		Anti-skin aging	*In vitro* (HaCaT cells) Expression of AQP3, FLG, INV and type 1 and 3 pro-collagen (↑)	
		Anti-inflammation	*In vitro* (RAW 264.7 cells) iNOS expression (↓) NO production (↓	
Chlorella vulgaris	A	Anti-atopic dermatitis	*In vivo* (NC/Nga mice) DFE-induced AD (↓) Epidermal thickness (↓) Skin hydration (↑) Infiltration of eosinophil and mast cell (↓) Serum chemokine levels of TARC and MDC (↓) mRNA level of IL-4, IFN-γ (↓)	[23]
Chlorella sorokiniana (ROQUETTE *Chlorella sp.*)	Spring water	Anti-skin inflammation	*In vivo* (hairless Skh-1 mice) TPA-induced skin inflammation (↓) macroscopic score (↓)	[24]
Chlorella	A	Anti-skin aging	Expression of MMP-1 (↓) type 1 pro-collagen / elastin (↑)	[25]
Chlorella vulgaris		Anti-skin cancer	*In vivo* DMBA-induced skin papillomagenesis (↓) Tumor burden (↓) Cumulative number of skin papillomas (↓) Percent incidence of mice bearing skin papillomas (↓)	[26]
Schizochytrium (ROQUETTE *Schizochytrium sp.*)	Spring water	Anti-skin inflammation	*In vivo* (hairless Skh-1 mice) TPA-induced skin inflammation (↓) Macroscopic score (↓)	[27]
Porphyra yezoensis (laver)	M	UV protection	*In vitro* (HaCaT cells) Cell viability (↑) Apoptosis (↓) Activation of JNK, ERK (↓)	[28]
Porphyra umbilicalis (Red algae) Vitamins,*Ginkgo biloba*	A	UV protection	*In vivo* (HRS/J-hairless mice) UVA/UVB-induced DNA damage (↓), erythema (↓), level of p53, caspase-3 (↓)	[29]
Furcellaria lumbricalis (brown algae)	A	Anti-skin aging	*In vitro* (HDFs) Expression of type 1	[30]

Fucus vesiculosus (red algae)			pro-collagen (↑)	
Spirulina maxima (blue algae) *Ulva lactuca* (green algae) *Lola implexa* (green algae) with other compounds		Anti-skin aging	*In vivo* (Human skin) Skin hydrating (↑) Skin firming effects (↑)	[31]

A: Aqueous extract, **E**: Ethanol extract, **M**: Methanol extract, **C**: Chloroform extract, **EAc**: Ethyl acetate extract, **PBS**: Phosphate-buffered saline, **w/o**: without, **Mg**: magnesium, **Ca**: calcium, **TYR**: tyrosinase, **DPPH:** 2,2-diphenyl-1-picrylhydrazy, **HEMs**: Human epidermal melanocytes**, HEKs**: Human epidermal keratinocytes, **HDFs**: Human dermal fibroblasts**, MMP-1**: Matrix Metalloproteinase-1, **TEWL**: Transepidermal water loss, **INV**: Involucrin , **LOR**: Loricrin, **TGM-1**: Transglutaminase-1, **FLG**: Filaggrin, **ORAC**: Oxygen radical absorbance capacity, **iNOS**: Inducible nitric oxide synthase, **NO**: Nitric oxide, **AQP3**: Aquaporin-3**, DFE**: *Dermatophagoides farinae* extract, **TARC**: thymus- and activation-regulated chemokine, **MDC**: macrophage-derived chemokine, **IL-4**: Interleukin-4, **IFN-γ**: Interferon-gamma, **TPA** : 12-O-Tetradecanoylphorbol-13-acetate, **DMBA**: 7,12-dimethylbenz [a] anthracene, **JNK**: c-Jun N-terminal kinase, **ERK**: Extracellular signal–regulated kinase, **HaCaT cells**: Spontaneously immortalized human keratinocytes

2.1.1. Macroalgal extracts

Cha *et al.* screened 43 indigenous marine algae for new skin whitening agents [16]. The aqueous extracts from brown algae *Endarachne binghamiae*, *Sargassum silquastrum*, *Ecklonia cava* and red algae *Schizymenia dubyi*, exhibited potent mushroom tyrosinase (TYR) inhibitory activity. Both *E. cava* and *S. silquastrum* reduced cellular melanin synthesis and TYR activity in a murine cell model and zebrafish model at non-toxcic concentration. Heo *et al.* recently screened 21 species of marine algae on melanogenesis using mushroom TYR activity [17]. Extracts of *Ishige okamurae Yendo* inhibited mushroom TYR activity and melanin synthesis in murine melanoma B16F10 cells.

According to Quah *et al.*, ethanol or hexane extract of brown algae including *Sargassum polycystum* and *Padina tenuis* significantly reduced mushroom TYR activity and melanin content in human epidermal melanocytes (HEMs) [18]. Topical application with ethanol or hexane extract of *S. polycystum* attenuated melanin production in guinea pigs in dermal irritation tests and de-pigmentation assessments. Hexane extract of *S. polycystum* was the most potent without totoxicity *in vitro* and *in vivo* models.

Murugan K *et al.* reported the anti-oxidant activity of extracts of brown, green and red marine algae. *In vitro* 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay and ferrous ion chelation were performed with methanol (M), chloroform (C), ethyl acetate (E), and aqueous (A) extracts of *Sargassum wightii* (brown algae), *Padina gymnospora* (brown algae), *Caulerpa peltata* (green algae) and *Gelidiella acerosa* (red algae) [19]. Non-polar C and E extracts showed higher DPPH radical-scavenging. However, A extracts (polar extracts) showed higher ferrous ion chelation. These results suggest that the anti-oxidant activity of marine algal extracts may have relieve skin aging and skin inflammation process that are affected by oxidative stress [32].

In 2002, Fujimura's group found that topical application of brown algae *Fucus vesiculosus* (Bladder wrack) aqueous extracts improved the thickness and elasticity of human cheek skin [20]. These results suggest that the *Fucus vesiculosus* extract possesses anti-aging activities and should be useful for a variety of cosmetics [20].

Previous study has shown the photoprotective effects of cosmetic formulations containing ultraviolet (UV) filters, vitamins, Ginkgo biloba and red algae *Porphyra umbilicalis* extracts *in vitro* and *in vivo* model [29]. Topical formulations including F (sunscreen formulation containing only UV filters), FA (sunscreen formulation with red algae extract) and FVGA (sunscreen formulation

with red algae extract, *G. biloba* and vitamins A, C and E) were applied on hairless mice. Extracts from the red algae PU could be considered effective ingredients to be used in sunscreen formulations. The combination of vitamins A, E, C and G. biloba along with red algae extracts can improve significantly the performance of the sunscreens, preventing UV-induced DNA damage and inflammation. Al-Bader T *et al.* reported the potential of anti-skin aging cosmetic ingredients containing red algae *Furcellaria lumbricalis* (black carrageen), brown algae *Fucus vesiculosus* [30]. Mixture of *F. vesiculosus* and *F. lumbricalis* extracts induced expression of type 1 pro-collagen in aged human dermal fibroblasts (HDFs). Another clinical study demonstrated anti-skin aging effects of *Spirulina maxima* (blue algae), *Ulva lactuca* (green algae), *Lola implexa* (green algae) with other compounds [31]. Marine algal mixtures ameliorated the skin hydrating and skin firming effects on human skin suggesting the utilization of marine algae in cosmeceuticals.

2.1.2. Microalgal extracts

Anti-skin aging and skin barrier function of microalgae extracts were assessed *in vitro* and *in vivo* [21]. Green-Blue microalgae, *Blue Lagoon coccoid Filamentous* were extracted with phosphate-buffered saline (PBS) without magnesium (Mg) and calcium (Ca). In human epidermal keratinocytes (HEKs), green-blue microalgae extracts increased expression genes of the transcriptional level of involucrin (INV), loricrin (LOR), transglutaminase-1 (TGM-1) and filaggrin (FLG) which are major markers for skin barrier function [33]. UV radiation upregulates collagen degradation through the increase of matrix metalloproteinase-1 (MMP-1) expression in HDFs. *Blue Lagoon* extracts suppressed MMP-1 upregulation and type 1 procollagen downregulation stimulated by UVA. Consistently, topical treatment of *Blue Lagoon* extracts (0.25% and 2.5%) reduced level of transepidermal water loss (TEWL) in human skin. Collectively, *Blue Lagoon* extracts improved skin barrier function and showed capacity to prevent premature skin aging.

Buono *et al.* demonstrated that aqueous extracts of *Botryococcus braunii* exhibited anti-oxidant, anti-skin aging and anti-inflammatory capacity in various cell-based model [22]. Skin aging is driven to oxidative stress in skin caused by intrinsic and extrinsic factors [32]. Oxygen radical absorbance capacity (ORAC) assay and COMET assay showed that intracellular reactive oxygen species (ROS) level and DNA damage were decreased by *B. braunii* extracts in NIH3T3 mouse embryo fibroblasts. Decreased levels of aquaporin-3 (AQP3) and FLG, INV and pro-collagen were observed in aged skin [34, 35]. *B. braunii* extracts treatment increased expression of AQP3, FLG, INV and type 1 and 3 pro-collagen in HaCaT cells, indicating potential anti-skin aging activity. Antioxidant activity is also closely related to anti-inflammatory process [32]. During inflammation, some pro-inflammatory cytokines and endotoxins induce the expression of an inducible nitric oxide synthase (iNOS), leading to the generation of nitric oxide (NO) in macrophages. Data revealed that *B. braunii* extracts significantly reduced lipopolysaccharide (LPS)-induced iNOS expression and NO production in murine macrophage RAW 264.7 cells. These results exerted that *B. braunii* water extract proved the biological activities concurring with the skin health maintenance.

Several studies described diverse beneficial effects of aqueous extracts of green microalgae *Chlorella* for skin health. Kang *et al. reported Chlorella vulgaris* attenuates *Dermatophagoides Farinae* (DFE)-induced atopic dermatitis (AD) in NC/Nga mice [23]. Hidalgo-Lucas S *et al.* reported that oral and topical administration of *Chlorella sorokiniana (*ROQUETTE *Chlorella sp.*) extracts improved on skin inflammation induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in hairless Skh-1 mice [24]. Previous study assessed the chemopreventive potential of *Chlorella vulgaris* against murine skin papillomagenesis [26]. Topical application of *C. vulgaris* (500 mg/kg b.w./day) significantly attenuated 12-dimethylbenz [a] anthracene (DMBA)-induced tumor size and number by up-regulating the sulfhydryl (-SH) and glutathlone S-transferase (GST) levels in skin tissues. The results indicated that marine algae could be utilized as preventive and therapeutic agents for various inflammatory skin diseases.

Recently, spring water extracts of *Schizochytrium* (ROQUETTE *Schizochytrium sp.*) were reported to exert anti-skin inflammatory poential *in vivo.* TPA-induced skin inflammation were significantly attenuated by oral administration (125, 250 and 500 mg/kg) and cutaneous application

(2.5, 5 and 10 %) with *Schizochytrium extracts* in Skh-1 hairless mice. However, further studies are required to examine the active ingredients and to understand detailed molecular mechanism(s) and direct target(s).

Kim *et al.* reported the modulatory ability of 80% methanol extract of *Porphyra yezoensis* (laver) on UVB-induced cell death in immortalized human keratinocyte, HaCaT cells [28]. The cell viability and apoptotic cells were increased and the ratio of reduced (GSH) to oxidized glutathione (GSSG) and the total glutathione content were decreased by post-treatment of *P. yezoensis* extract enhanced UVB-induced downregulation of c-Jun N-terminal kinase (JNK) and extracellular signal–regulated kinase (ERK) signaling pathways resulting in decrease of apoptotic damage. The result indicates that *P.yezoensis* extract can protect skin cells from UVB damage, contributing to improving of skin health.

2.2. Biological activities of polysaccharides from marine algae

Marine algae are abundant in polysaccharides such as fucoidans in brown algae, ulvans in green algae and carrageenans in red algae [36]. Skin beneficial effects of polysaccharides from marine algae were summarized in table 2 along with species, biological function and mechanism of action.

Table 2. Bioactive functions of marine algal polysaccharides

Species	Saccharides	Function	Mechanism	Ref
	Fucoidan	Anti-melanogenesis	*In vitro* (Mel-Ab cells) Activation of ERK (↓) Melanin content (↓)	[37]
Sargassum tenerrimum *Turbinaria conoides*	Fucoidan	Anti-oxidant	*In vitro* DPPH radical (↓) Superoxide radical (↓) High total antioxidant and FRAP ability	[38-41]
Costaria costata	Fucoidan	Anti-skin aging	*In vitro* (HS68 cells) UVB-induced mRNA and pro-tein expression of MMP-1 (↓) type 1 pro-collagen (↑) Activation of EKR, JNK (↓)	[42, 43]
	Fucoidan		*In vitro* (HaCaT cells) Expression of MMP-1 (↓) type 1 pro-collagen (↑)	[44]
Mekabu	Fucoidan		*In vivo* UVB-induced edema (↓) Thickness of prickle cell layer (↓) MMP-1 activity & expression, IFN-◎◎(↓)	[45]
Ascophyllum nodosum	Fucoidan (16kDa) by acidic hydrolysis		*In vitro* (HDFs) IL-1β-induced MMP-9, MMP-3 expression/ secretion (↓) TIMP-1 (↑)	[46]

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			Ex vivo (human skin) Elastic fiber degradation (↓) Leukocyte elastase activity (↓)	
Laminaria cichorioides	Fucoidan	Anti-atopic dermatitis	*In vivo* (Nc/Nga mice) DNCB-induced AD (↓) Clinical severity scores (↓) Scratching counts (↓) Epidermis thickness (↓) Mast cell count (↓) Infiltration of mast cells (↓) Serum histamine (↓) Total IgE (↓)	[47]
			in vitro (Human keratinocytes) AD-associated chemokines TARC, MDC, RANTES (↓)	
	Fucoidan		*Ex vivo* IgE production in PBMC from patients with AD (↓) Immunoglobulin germline transcripts of B cells (↓) IgE-secreting cells count (↓)	[48]
Saccharina japonica	Fucoidan	Moisturizing	Higher moisture-absorption and moisture-retention ability than HA	[49]
Laminaria cichorioides	Fucoidan (water soluble)	Anti-skin cancer	*In vitro* (JB6 Cl41 cells) EGF or TPA-induced neopla-stic cell transformation (↓) Binding of EGF and EGFR (↓)	[50]
Saccharina longicruris	Laminaran	Anti-skin aging	*In vivo* (Kunming SPF mice) UVA+UVB-induced skin dermal thickness (↓) Hyp content (↑) Serum or mRNA level of MMP-1 (↓), TIMP-1 (↑)	[51]
		Dermal tissue-engineered production	Deposition of matrix (↑)	[52]
Ulva pertusa	Ulvans	Anti-oxidant	*In vitro* Superoxide (↓) Hydroxyl radicals (↓) Reducing power (↑) Metal chelating ability (↑)	[53]
	Acetylated and benzoylated ulvans			[54]
Ulva sp.	Crude ulvans (57kDa) LMW ulvan	Anti-skin aging	*In vitro* (HDFs) Hyaluronan production Collagen release (-)	[55]

	(4kDa)			
Porphyra sp.	Porphyran	Anti-oxidant	*In vitro* Ferrous ion chelating Reducing power (↑) DPPH radical (↓) Superoxide (↓)	[56]
Porphyra haitanensis	Porphyran fraction F1 fraction F2		*In vivo* (Kumming mice) Antioxidant enzyme activity such as MDA (↓), SOD (↑), GSH-Px (↑) lipid peroxidation (↓) TAOC in different organs (↑)	[57, 58]
	Porphyran with different MW		*In vitro* DPPH radical (↓) Reducing power (↑)	[59]
	LMW Porphyran SD, AD, PD, BD		*In vitro* DPPH radical (↓) Hydroxyl radicals (↓) Superoxide (↓)	[60]
Porphyra yezoensis	Porphyran	Anti-inflammation	*In vitro* (RAW264.7 cells) LPS-induced NO, iNOS level, NF-κB activation, TNF-α, nuclear translocation of p65, phosphorylation and degradation of IκB-α (↓)	[61, 62]
Porphyridium	Carrageenan	Anti-melanogenesis	*In vivo* (Guinea pig) Level of melanosome (↓)	[63]
Commercial	ι(II)-Carrageenan	Anti-oxidative Photoprotective	*In vitro* (HaCaT cells) UVB-induced cell death (↓) DCF-DA: Intracellular ROS (↓) DPPH radical (↓)	[64]
Eucheuma spinosum (Eucheuma denticulatum)	ι(V)-Carrageenan			
Commercial	λ-Carrageenan			
Eucheuma cottonii (Kappaphycus alvarezii)	κ(III)-Carrageenan			
Commercial	ι(II)-Carrageenan			
	κ-COSs (37.7 kDa)	Anti-oxidant	*In vitro* Superoxide radical (↓) Hydroxyl radical (↓) DPPH radical (↓) Reducing power (↑)	[65]
	κ-COSs (1.2 kDa) SD (0.8 kDa) LAD (1.2 kDa) HAD (1.4 kDa		*In vitro* Superoxide (↓) Hydroxyl radical (↓) DPPH radical (↓) Reducing power (↑)	[66, 67]

	PD (1.1 kDa)		Iron ion chelation (↑) Total antioxidant activity (↑)	
	κ-COSs with CP	Photo-protective	*In vitro* (HaCaT cells, MEFs) UVB-induced damage (↓)	[68]

Mel-Ab cells: Spontaneously immortalized murine melanocyte cell line, **ERK**: Extracellular signal–regulated kinase, **DPPH**: 2,2-diphenyl-1-picrylhydrazy, **FRAP**: ferric reducing antioxidant power, **HS68 cells**: Human foreskin fibroblast, **UV**: Ultraviolet, **MMP-1**: Matrix metalloproteinase-1, **JNK**: c-Jun N-terminal kinase, **IFN-⚜**: Interferon-gamma, **IL-1β**: Interleukin-1β, **MMP-9**: Matrix metalloproteinase-9, **MMP-3**: Matrix metalloproteinase-3, **TIMP-1**: Tissue inhibitor of metalloproteinases inhibitor 1, **DNCB**: 2,4-Dinitrochlorobenzene, **AD**: Atopic dermatitis, **IgE**: Immunoglobulin E, **TARC** : Thymus- and activation-regulated chemokine, **MDC** : Macrophage-derived chemokine, **RANTES** : Reg ulated upon activation, normal T-cell expressed and secreted chemokine, **EGF**: Epidermal growth factor, **TPA** : 12-O-Tetradecanoylphorbol-13-acetate, **EGFR**: Epidermal growth factor receptor, **IP** : Intraperitoneal injection (abdominal injection), **SPF**: Specific pathogen free, **Hyp**: hydroxyproline, **LMW**: Low molecular weight, **HaCaT cells**: Spontaneously immortalized human keratinocytes, **kappa (κ), iota 2 [ι(II)], iota 5 [ι (V)], lambda (λ) kappa [κ(III)], DCF-DA**: 2′,7′-dichlorofluorescin diacetate, **ROS**: Reactive oxygen species, **SD**: sulfated derivatives, **LAD**: lowly derivatives, **HAD**: highly acetylated derivatives, **AD**: acetylated, **PD**: phosphorylated derivatives, **BD**: benzoylated derivatives, **COSs**: Carrageenan oligosaccharides, **CP**: Collagen peptide, **JB6 cells**: mouse epidermal cells, **MEFs**: Mouse embryonic fibroblasts, **HA**: Hyaluronic acid, **MDA**: Malondialdehyde, **SOD**: Superoxide dismutase, **GSH-Px**: Glutathione peroxidase, **TAOC**: total antioxidant capacity

2.2.1. Fucoidans

Fucoidans are major sulfated polysaccharides (SPs) found in the cell wall of some brown algae [10]. A numerous studies have reported the skin benefits of fucodian against diverse skin disorders including pigmentation, skin aging, atopic dermatitis and skin carcinogenesis.

2.2.1.1. Anti-melanogenic activity

Kang *et al*. documented that fucoidan reduced melanin content by activating ERK pathway in Mel-Ab Cells [37]. While fucoidan treatment did not directly decrease TYR activity, but downregulated microphthalmia-associated transcription factor (MITF) and TYR protein expression.

2.2.1.2. Antioxidant activity

In vitro antioxidant capacities of fucoidan from *Sargassum tenerrimum* was analyzed by DPPH, superoxide radical scavenging and total antioxidant assays [41]. Antioxidant activity of SPs depends on their structural properties such as level or distribution of sulfate groups, MW, sugar composition, and stereochemistry [36]. Consistent results were documented that fucoidan from brown algae *Laminaria japonica* possessed high superoxide radical and hydroxyl radical scavenging assays according to sulfate content [39, 40]. Fucoidans from *Fucus vesiculosus* exhibited considerable ferric reducing antioxidant power (FRAP) [38] and superoxide radical scavenging property [69].

2.2.1.3. Anti-skin aging activity

A study conducted by Moon *et al.* reported that fucoidan from *Costaria costata* showed anti-skin aging activity in human foreskin fibroblasts HS68 cells [42, 43] and HaCaT cells [44]

Fucoidan suppressed mRNA and protein expression of MMP-1 upregulation and type 1 pro-collagen downregulation stimulated by UVB via inactivation of EKR and JNK. Additionally, fucoidan from *Mekabu* inhibited Interleukin-1β (IL-1β)-induced secretion of MMP-9, -3 and degradation of tissue inhibitor of metalloproteinases inhibitor 1 (TIMP-1) in HDFs [46]. In addition, a positive correlation has reported that UVB-induced edema, thickness of prickle cell layer, MMP-1 activation and interferon (IFN)-γ were attanuated by fucoidan treatment on mice skin [45]. Senni *et*

al. demonstrated that fucoidan (16kDa) from *Ascophyllum nodosum* by acidic hydrolysis exhibited anti-skin aging potential in human skin via preventing elastic fiber degradation and leukocyte elastase activity [46]. These results indicate that fucodians represented the anti-skin aging potential with varied mechanisms of action.

2.2.1.4. Anti-atopic dermatitis activity

Fucoidan from *Laminaria cichorioides* alleviated 2,4-dinitrochlorobenzene (DNCB)-induced AD *in vitro* and *in vivo* model [47]. AD-associated chemokines including thymus- and activation-regulated chemokine (TARC), macrophage-derived chemokine (MDC) and reg ulated upon activation, normal T-cell expressed and secreted chemokine (RANTES) were inhibited by fucoidan treatment in Human keratinocytes. Another study reported that *ex vivo* anti-atopic dermatitis of fucoidan inhibited IgE production in peripheral blood mononuclear cell (PBMC) from patients with AD, immunoglobulin germline transcripts of B cells and IgE-secreting cells count [48]. Thus, fucoidan would contribute to develop preventive and therapeutic agents for skin inflammatory disease such as AD.

2.2.1.5. Moisturizing activity

Previously, *Saccharina japonica* extracts from brown algae showed profound ability of moisture retention than other kinds of algae [6]. Particularly *S. japonica* polysaccharides were identified as better humectant than hyaluronic acid (HA or called hyaluronan),which has the ability of retaining a large amount of water [49], followed red macroalgae extracts. Other extracts from green algae showed lower water retention capacity than HA. Therefore, SPs from marine algae, especially fucoidan have potential as humectants against skin dehydration.

2.2.1.6. Anti-skin cancer activity

The chemopreventive activity and the underlying molecular mechanisms of fucoi-dan from *Laminaria cichorioides* was elucidated by Lee *et al.* in 2008. Water soluble fucoidan from *L. cichorioides* were treated upto 100 μg/mL and were not cytotoxice in JB6Cl41 mouse epidermal cells. Fucoidan inhibited the epidermal growth factor (EGF) or TPA-induced neoplastic cell transformation through preventing the binding of EGF to its cell surface receptor (EGFR) [50]. These evidences suggested that molecular mechanism of anti-skin carcinogenic action of fucoidan with potential application for chemopreventive agents.

2.2.2. Laminaran

Laminaran (also known as laminarin) is one of major non-SP found in brown algae. Biological activities of fucoidans have been well-studied, while those of laminaran have poorly understood to date. Laminaran from brown algae *Saccharina longicruris* has been reported to show the anti-skin aging induced by UVA/UVB i*n vivo* model [51]. Kumming mice is an experimental animal model reflecting age-related decline characteristics of female fertility in human [70]. UV irradiation facilitated the process of extrinsic aging as well as intrinsic aging. Intraperitoneal (IP) injection of laminaran (1 or 5 mg/kg) attenuated UVA/UVB-induced skin dermal thickness by downregulating MMP-1 and upregulating TIMP-1 and hydroxyproline (Hyp) content. Ayoub *et al.* demonstrated that laminaran from *Saccharina longicruris* prevented deposition of matrix [52]. Considering these results, laminaran may contribute to the prevention of the progression of skin aging.

2.2.3. Ulvans

Ulvans are sulfated heteropolysaccharides extracted from the cell wall of green algae *Ulva pertusa* [53]. Ulvans are water-soluble sulfated polysaccharides and the main constituents of ulvan are rhamnose, xylose, glucose, uronic acid and sulfate. They also identified that glucuronic acid and rhamnose occur mainly in the form of the aldobiouronic acid, 4-O-β-d-glucuronosyl-l-rhamnose

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[71]. Due to the high recalcitrance of ulvan which is related with the complex chemical structure, their biological functions have less exploited.

Radical scavenging assay revealed that antioxidant, reducing activity and ferrous ion chelating ability of ulvans were proportionate to sulfate content [53]. High sulfate content showed more profound anti-oxidant properties [53]. Followed study reported that low molecular weight (LMW) and high sulfate content derivatives of ulvans showed enhanced antioxidant activities [36]. In addition, the antioxidant activity of acetylated and benzoylated ulvans was stronger than that of natural ulvan [54]. Recently, SPs including crude ulvans (57kDa) and LMW ulvan (4kDa) were isolated from *Ulva sp*. and their anti-skin aging activities were evaluated [55]. HA production was significantly upregulated by SPs of from *Ulva sp* in HDFs. Crude ulvans (57kDa) showed stronger stimulatory activity of HA production than LMW ulvan (4kDa). These findings revealed the biological activities of ulvans and may account for the development of skin beneficial ingredients from marine algae.

2.2.4. Porphyran

Red algae *Porphyra* is edible seaweed food well-known as laver, gim (Korean) or nori (Japanese). Porphyra is the mainly composed of porphyran which is the sulfated polysaccharide comprising the hot-water soluble portion of cell wall [59]. Porphyran is related to agarose in that it contains disaccharide units consisting of 3-linked β-d-galactosyl residues alternating with 4-linked 3,6-anhydro-α-L-galactose, but differs in that some residues occur as the 6-sulfate [58].

2.2.4.1. Anti-oxidant activity

Porphyran have been reported to scavenge oxidative radicals *in vitro* [56], increase antioxidant enzymes activity and antioxidant capacity in aging mice [57, 58].

Porphyran from *Porphyra sp.* aqueous extract showed significant ferrous ion chelating capacity and reducing power [56]. In addition, DPPH radical and superoxide radical were dose-dependently quenched by porphyran treatment. Zhao *et al*. [59] found that the porphyrans from *Porphyra haitanensis* with different MW showed different antioxidant activities. Assays including DPPH radical and reducing power indicated that porphyrans with lower MW exhibited the higher antioxidant activities. According to following study, the LMW porphyran and its different derivatives were determined the relationship between antioxidant activity and chemical modifications [60]. Sulfated (SD), acetylated (AD), phosphorylated (PD) and benzoylated (BD) derivatives of porphyran from *P. haitanensis* showed higher antioxidant activities *in vitro* than that of LMW porphyran. Among diverse derivatives, the BD exerted the most excellent antioxidant activities in DPPH radical, hydroxyl radicals and superoxide scavenging assays. These results also support that the antioxidant activity of polysaccharide is closely related to several structural elements such as MW, degree of substitution (DS) and functional groups [60].

In vivo antioxidant activity of porphyran fraction F1 [58] and F2 [57] derived from *P. haitanensis* has been assessed in aging mice [36]. Kumming mouse is an animal model exhibiting features related with an age-related decline [70]. Malondialdehyde (MDA) is a main marker of endogenous lipid peroxidation. According to aging, the organs significantly increased level of MDA indicating that peroxidative damage increases with the aging process [57, 58]. IP administration of porphyran fraction F1 (50, 100 and 200 mg/kg) and F2 (100, 200 and 400 mg/kg) significantly decreased the MDA level in aging mice indicating prevention effect of lipid peroxidation. Superoxide dismutase (SOD) is an intracellular antioxidant enzyme that protects against oxidative processes initiated by the superoxide anion [58]. Glutathione peroxidase (GSH-Px) is enzymatic antioxidant defense system to protect oxidative damage, while total antioxidant capacity (TAOC) reflects the capacity of the non-enzymatic antioxidant defense system [58]. Porphyran franction F1 and F2 both increased the TAOC and upregulated activity of SOD and GSH-Px in Kumming aging mice suggesting their significant *in vivo* anti-oxidant activity [57, 58].

2.2.4.2. Anti-skin inflammatory activity

Porphyran from *Porphyra yezoensis* showed the anti-inflammation activity in LPS-stimulated macrophages [61]. Porphyran suppressed LPS-induced NO production and iNOS level by the blocking of nuclear factor kappa B (NF-κB) activation in RAW264.7 cells. Porphyran reduced LPS-induced NF-κB activation via inhibiting nuclear translocation of p65, phosphorylation and degradation of inhibitor of kappa B (IκB)-α in RAW264.7 cells. Meanwhile, porphyran showed moderate inhibitory effect on LPS-induced tumor necrosis factor (TNF)-α production in RAW264.7 cells. These results suggest that porphyran blocked LPS-induced NO production via inactivation of NF-κB in murine macrophage cells.

2.2.5. Carrageenan

Carrageenan from red algae is linear SP composed of 3,6-anhydro-D-galactose (D-AHG) and D-galactose. Carrageenan has been utilized in cosmetic products as stabilizer, emulsifiers and moisturizer due to its chemical and physical properties. Besides, carrageenan is known to exhibit various beneficial effects on skin health and summarized in table 2.

2.2.5.1. Anti-melanogenic activity

Carrageenan from red microalgae *Porphyridium,* has been reported as macrophage toxic substances [63]. Injection of carrageenan effectively degraded and eliminated dermal melanosomes/melanin from the dermis of guinea pigs indicating that skin whitening potential of carrageenan.

2.2.5.2. Anti-oxidant activity

Thevanayagam *et al.* assessed the photoprotective and anti-oxidative activities of various isoforms of carrageenan in HaCaT cells [64]. Carrageenan iota 2 [ι (II)], iota 5 [ι (V)] from *Eucheuma spinosum*, lambda (λ) and kappa (κ) type III from *Eucheuma cottonii*. Commonly, all types of carrageenan can scavenge free radicals, however, *in vitro* anti-oxidant capability did not correlate with the amount of sulphur moieties in the different isomers. Although κ-carrageenan contained the least sulphate content compared to ι- and λ-carrageenan, κ-carrageenan exhibited the highest radical scavenging activity. The DPPH reducing capability of carrageenan followed the order λ< ι < κ. These evidences indicate that increase in oxidative property with irradiation dose can be attributed mainly to the depolymerization of the carrageenan with corresponding increase in reducing sugar. In addition, the presence of the hydrophobic 3,6-anhydrogalatose could affect the antioxidant activity of carrageenan.

Other studies investigated the anti-oxidant capacity of κ-carrageenan, κ-carrageenan oligosaccharides (κ-COSs) and their chemically modified derivatives including oversulfated (SD, 0.8kDa), lowly (LAD, 1.2kDa), highly acetylated (HAD, 1.4kDa) and phosphorylated derivative (PD, 1.1kDa) [65-67]. As *in vitro* antioxidant activity assay, it was performed that reducing power, iron ion chelation, and total antioxidant activity. Generally, chemical modification of COSs can enhance their antioxidant activity *in vitro* as followed PD>SD>LAD>, HAD [67]. In this study, sulfate contents seem to be related with antioxidant activity. Taken together, these investigations indicate that antioxidant properties of carrageenans have close relation with sulfate content structure as well as type of sugar unit and DPs according to MW.

2.2.5.3. Photoprotective activity

Ren *et al.* reported the anti-oxidative and photoprotective effect of complex of κ-COSs and collagen peptide (CP) in HaCaT cells and mouse embryonic fibroblasts (MEFs) [68]. Complex of κ-COSs and CP (100 μg/mL) could significantly attenuate UV-induced cell death and apoptosis in HaCaT and MEF through reduction of intracellular ROS level. Complex of κ-COSs and CP almost inhibited UV-induced decrease of type 1 pro-collagen and increase of MMP-1 by suppressing

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MAPKs signaling pathway. Collectively, complex of κ-COSs and CP may have photoprotective potential against skin aging.

2.3. Biological activities of monosaccharides and oligosaccharides from red algae

Agar is the major polysaccharides of red macroalgae. Agar is easily hydrolyzed into oligosaccharides by various chemical and enzymatic methods [72]. Depending on the hydrolysis method, oligosaccharides with different DPs can be generated from agar [73]. Agarose-derived oligosaccharides are referred as agarooligosaccharides (AOSs). There are two forms of AOSs including neo-form and agaro-form. Neo-form of AOSs are called as neoagarooligosaccharides (NAOSs) which have repeating neoagarobiose units composed of D-galactose at the non-reducing end and 3,6-anhydro-L-galactose (L-AHG) at the reducing end. Table 3 shows the beneficial effects of monosaccharides and oligosaccharides from red algae.

Table 3. Bioactive functions of marine algal monosaccharides and oligosaccharides

DP	Name	Mode of Linkage	Function	Mechanism	Ref
1	D-Glucose	-	Anti-melanogenesis	*In vitro* (B16 cells) TYR activity (↓) Melanin content (-)	[74]
	L-AHG	-		*In vitro* (B16F10 cells or HEMs) Melanin content (↓), TYR activity (-)	[75, 76]
	D-AHG	-	Anti-inflammation	*In vitro* (Raw264.7 cells) LPS-induced NO level (↓)	[76]
	D-Galactose	-	Melanogenesis	*In vitro* (B16 cells) Melanin content (-) TYR activity (↑)	[74, 76]
2	Agarobiose	$Gal_{\beta1\rightarrow4}AHG$	Anti-oxidant	*In vitro* DPPH radical (↓)	[77]
			Anti-inflammation	*In vitro* (RAW264.7 cell) LPS-induced level of NO, PGE2 (↓) Expression of HO-1 (↑) Protein level of iNOS (↓)	[78]
				In vitro (Human Monocytes) LPS-induced Cytokines TNF-α, IL-1b, IL-6 (↓)	
				In vitro (Human Monocytes) LPS-induced NO level (↓) mRNA level of COX-2, mPGES-1 (↓)	[79]
	Neoagarobiose	$AHG_{\alpha1\rightarrow3}Gal$	Anti-melanogenesis	*In vitro* (B16 cells) Melanin content (↓) Cellular TYR activity (↓)	[80, 81]
			Moisturizing	Higher moisture-absorption and moisture-retention ability than HA	

3	Agarotriose	Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal	N.a.	-	-
	Neoagarotriose	AHG$_{\alpha1\rightarrow}$ $_{3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG	N.a.	-	-
4	Agarotetraose	Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG	Anti-oxidant	*In vitro* DPPH radical (↓)	[77]
			Anti-inflammation	*In vitro* (RAW264.7 cell) LPS-induced level of NO (↓)	[78]
	Neoagarotetraose	AHG$_{\alpha1\rightarrow}$ $_{3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal	Anti-melanogenesis	*In vitro* (B16 cells or HEMs) Melanin content (↓) Cellular TYR activity (↓)	[75, 82]
5	Agaropentaose	Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal	N.a.	-	-
	Neoagaropentaose	AHG$_{\alpha1\rightarrow}$ $_{3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG	N.a.	-	-
6	Agarohexaose	Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG	Anti-oxidant	*In vitro* DPPH radical (↓)	[77]
			Anti-inflammation	*In vitro* (RAW264.7 cell) LPS-induced level of NO (↓)	[78]
				In vitro (Human Monocytes) LPS-induced NO level (↓) mRNA level of COX-2, mPGES-1 (↓)	[79]
	Neoagarohexaose	AHG$_{\alpha1\rightarrow}$ $_{3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal	Anti-melanogenesis	*In vitro* (B16 cells or HEMs) Melanin content (↓) Cellular TYR activity (↓)	[75, 82, 83]
7	Agaroheptaose	Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal	N.a.	-	-
	Neoagaroheptaose	AHG$_{\alpha1\rightarrow}$ $_{3}$Gal$_{\beta1\rightarrow}$ $_{4}$AHG$_{\alpha1}$ $_{\rightarrow3}$Gal$_{\beta1\rightarrow}$	N.a.	-	-

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		$_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG			
8	Agarooctaose	Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG	Anti-oxidant	*In vitro* DPPH radical (↓)	[77]
	Neoagarooctaose	AHG$_{\alpha1\rightarrow}$ $_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal	N.a.	-	-
9	Agarononaose	Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal	N.a.	-	-
	Neoagarononaose	AHG$_{\alpha1\rightarrow}$ $_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG	N.a.	-	-
10	Agarodecaose	Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG	Anti-oxidant	*In vitro* DPPH radical (↓)	[77]
	Neoagarodecaose	AHG$_{\alpha1\rightarrow}$ $_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$ $\rightarrow_3$Gal$_{\beta1\rightarrow}$ $_4$AHG$_{\alpha1}$	N.a.	-	-

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		→3Galβ1→4AHGα1→3Galβ1→4AHGα1→3Gal			
-	Mixture of AOSs with DP 2, 4, 6 and 8	[Galβ1→4AHG]n	Anti-melanogenesis	*In vitro* (B16 cells) Melanin content (↓) Cellular TYR activity (↓)	[83]
			Anti-skin cancer	*In vivo* (ICR mice) DMBA/TPA-induced tumor incidence (↓), number of papilloma (↓), TPA-induced ear edema (↓) TPA-induced PGE2 (↓)	[79]
			Anti-inflammation	*In vitro* (Human monocytes) LPS-induced NO level (↓)	

DP: Degree of polymerization, **TYR**: Tyrosinase, **B16(F10) cells**: Mouse melanoma B16(F10) cells, **(-)**: Not effective, **L-AHG**: 3,6-Anhydro-L-galactose, **HEMs**: human epidermal melanocytes, **D-AHG**: 3,6-Anhydro-D-galactose, **DPPH**: 2,2-diphenyl-1-picrylhydrazy, **LPS**: Lipopolysaccharides, **NO**: Nitric oxide, **PGE2**: Prostaglandin E2, **HO-1**: heme oxygenase-1, **iNOS**: Inducible nitric oxide synthase, **TNF**: tumor necrosis factor, **IL**: Interleukin, **COX-2**: Cyclooxygenase-2, **mPGES-1**: Microsomal prostaglandin E synthase-1, **N.a.**: Not applicable, **AOSs**: Agaro-oligosaccharides

2.3.1. Anti-melanogenic activity

Previous studies have reported that the NAOSs with different DPs including neoagarobiose (NeoDP2), neoagarotetraose (NeoDP4) and neoagarohexaose (NeoDP6) had a whitening effect and inhibited TYR activity in the murine melanoma B16F10 cells [81-83]. NAOSs with different DPs were not cytotoxic to B16F10 up to 100 μg/mL showing that their skin whitening effect were not derived from affecting cell viability. In addition, NeoDP4 and NeoDP6 reduced extracellular melanin contents in B16F10 cells and pigmentation eveluated by Fontana-Masson staining in HEMs, whereas agarotriose (DP3), agaropentaose (DP5) and agaroheptaose (DP7) did not reduced melanin productoin [75].

Recent studies have reported that oligosaccharides from agarose showed anti-melanogenic activity according to the DP of the galactosyl groups [84]. D-glucose and D-galactose are common mono-saccharides of marine algae. L-AHG is major components of agar, while D-AHG is a major monomeric sugar unit of carrageenan from red macroalgae. Previously, effects of monosaccharides including L-AHG, D-AHG and D-galactose on α-MSH-induced melanin production in B16F10 melanoma cells have been reported [75, 76]. Melanin level was significantly suppressed by 100 μg/mL of L-AHG. D-AHG also showed inhibitory effect on melanin production only at 100 μg/mL, but its effect was slightly lower than that of L-AHG. Other monomeric sugar, D-galactose, did not affect any significant reduction in the melanin production in B16F10 cells. In addition, previous study reported that TYR activity was promoted by D-galactose, but it seems like to being decreased in the presence of glucose [74]. In addition, D-glucose also did not affect melanin content in murine melanoma cells [74]. Furthermore, a recent study have demonstrated that L-AHG suppresses melanogenic proteins via inhibiting cyclic adenosine monophosphate/cyclic adenosine monophosphate-dependent protein kinase, MAPK, and Akt signaling pathways in HEMs [85]. Collectively, red macroalgal sugars such as L-AHG and D-AHG showed anti-melanogenic activity and considered as active components of red macroalgae for skin whitening activity.

2.3.2. Anti-skin inflammatory activity

It has reported that effect of L-AHG on LPS-induced NO production in RAW264.7 cells [76]. To our knowledge, this was first report of the biological activity of L-AHG. Nitrite production was significantly suppressed by 100 and 200 μg/mL of L-AHG. D-AHG showed a nitrite-suppressing effect only at 200 μg/mL, but its effect was significantly lower than that of L-AHG. Other saccharides, such as NeoDP2 and D-galactose, did not induce any significant reduction in the nitrite production of RAW264.7 cells.

Enoki T *et al.* reported the anti-inflammatory activities of AOSs including agarobiose (DP2), agarotetraose (DP4) and agarohexaose (DP6), having L-AHG at the reducing end. Agarobiose (DP2), agarotetraose (DP4) and agarohexaose (DP6) dose-dependently suppressed NO production in RAW264.7 cells. Meanwhile, neo-agarohexaose (DP6), having D-galactose at the reducing end, had no inhibitory effect on nitrite production. Agarobiose (DP2) suppressed LPS-induced prostaglandin E2 (PGE2), and pro-inflammatory cytokine levels in activated monocytes/macrophages via heme oxygenase-1 (HO-1) induction.

Latter study conducted by Enoki T *et al*. demonstrated the anti-inflammatory effects of AOSs mixture with DP 2, 4, 6 and 8 in human monocytes [79]. AOSs mixture attenuated LPS-induced NO level in human monocytes. Agarobiose (DP2), agarohexaose (DP6) decreased LPS-induced mRNA level of COX-2, mPGES-1 in human monocytes. However, it is currently unclear whether AOSs can elicit anti-inflammatory activity *in vivo* by contacting activated monocytes/machrophages at an inflammation site, since a high dose of AOSs was needed to inhibit the release of pro-inflammatory mediators in an *in vitro* study.

2.3.3. Anti-oxidant activity

Ajisaka K *et al.* compared the anti-oxidative potency of various carbohydrates including fucoidan and AOSs [86]. In DPPH assay, fucoidan showed remarkable radical scavenging activity, although lower than ascorbic acid, but AOSs almost did not have DPPH radical scavenging activity up to 20 mM. However, the SOD activity assay revealed that AOS had high antioxidant activity notably showing almost half of the anti-oxidant activity of ascorbic acid.

Chen HM *et al.* evaluated the antioxidant activity of AOSs with different DPs in cell-based system [77]. *In vitro* DPPH assay revealed that agarohexaose showed the highest radical scavenging capacity. Intracellular ROS level was investigated by using the dichlorofluorescein (DCF) assay in L-02 human liver cell. Agarohexaose at 1 mg/mL significantly reduced H_2O_2-induced oxidants up to 50% showing the highest scavenging capability. In conclusion, AOSs could be novel antioxidants which could protect cell damage caused by ROS, especially agarohexaose exhibiting most excellent effects.

2.3.4. Moisturizing activity

Previously, NeoDP2 has been reported to show not only whitening effects but also moisturizing effects [81]. NeoDP2 showed a higher hygroscopic ability than glycerol or HA, typical moisturizing reagents, indicating that algae-derived saccharides could be used as a moisturizer in cosmetics.

2.3.5. Anti-skin cancer activity

Previously, it has been reported the ability of AOSs from red macroalgae to prevent tumor promotion on the two-stage mouse skin carcinogenesis model [79]. AOSs feeding led to delayed DMBA/TPA-induced tumor incidence and tumor number in ICR mice. PGE2 production was also suppressed by AOSs intake in TPA-induced ear edema model. AOSs down-regulated cyclooxygenase-2 (COX-2) and microsomal PGE synthase-1 (mPGES-1), rate-limiting enzymes in PGE2 production, in human monocytes. Consequently, AOSs are expected to prevent tumor promotion by inhibiting PGE2 elevation in chronic inflammation site.

3. Concluding remarks

In this review, we have provided that various biological activity of marine algae extracts and marine algal carbohydrates as novel cosmeceuticals. Marine algae extracts and carbohydrates were categorized by source (species), structural parameters, bioactive functions and mechanism. Numerous *in vitro* and *in vivo* studies showed that marine algae extracts and algal carbohydrates showed various biological activity against skin disorders including hyperpigmentation, winkle, dehydrated skin disease, skin inflammation and skin cancer. However, although diverse biological activities of marine carbohydrates have been determined, their detailed molecular mechanisms and target proteins are not fully understood. Therefore, further investigations should elicit the precise molecular basis of marine algal compounds for biological activity. Understanding of marine algal carbohydrates and their skin benefits would contribute to develop the noble cosmeceuticals.

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