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Fucoxanthin: A Natural Treasure from The Sea with Dual Benefits - Antioxidant and Anti-melanogenic Activities

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ABSTRACT

Whitening cosmetics with anti-melanogenesis activity are widely popular globally. Numerous studies are underway to identify new ingredients exhibiting anti-melanogenesis effects for the development of novel products. There has been a notable surge in the utilization of natural anti-hyperpigmentation agents sourced from marine origins for both pharmaceutical and cosmetic applications. This review aims to provide an overview of the antioxidant and anti-melanogenesis effect of brown seaweed which harbors a significant quantity of fucoxanthin, serving as a skin whitening agent. Secondary metabolites derived from brown algae have also been harnessed for use in cosmetics. However, many of the reviewed articles lack comprehensive investigations into molecular targets, essential for fulfilling the criteria of cosmetic and pharmaceutical utilization. Recently, various secondary metabolites, particularly carotenoids like fucoxanthin, have been identified from brown seaweed, demonstrating anti-melanogenesis properties and underlying mechanisms. Nevertheless, *in vivo* and clinical investigations of marine algae-derived whitening agents remain scarce. The novelty of this review lies in the discourse surrounding fucoxanthin as a major carotenoid in brown algae, highlighting its antioxidant and anti-melanogenesis potential. An anti-melanogenesis test is generally preceded by an antioxidant activity test. Almost all brown algae exhibit notable antioxidant effect compared to control, suggesting inherent antioxidant properties. In addition, the melanogenesis effect of brown algae surpasses that of controls. In the future, fucoxanthin compounds hold promise for incorporation into cosmetics within the pharmaceutical industry.

Keywords: Brown algae, secundery metabolite, melanogenesis, tyrosinase, whitening, cosmetics.

INTRODUCTION

Brown seaweed, also known as brown algae, is a type of marine plant that has gained widespread attention in various regions around the world, particularly in Asia (NASER, 2021). The abundance of marine algae in Asian waters is due to the high exposure to sunlight that the ocean receives, creating ideal conditions for these marine plants to thrive (Rosales-Mendoza *et al.*, 2020; Tabakaev *et al.*, 2021). This abundance has led to the utilization of brown seaweed in a wide range of contexts, spanning various industries and applications, accompanied by a growing recognition of its health benefits and resource potential (Müller *et al.*, 2011). Furthermore, research endeavors have illuminated the promising health advantages attributed to fucoxanthin, particularly in its capacity to mitigate chronic conditions such as cancer, obesity, diabetes mellitus, and liver disease (Zhang *et al.*, 2022).

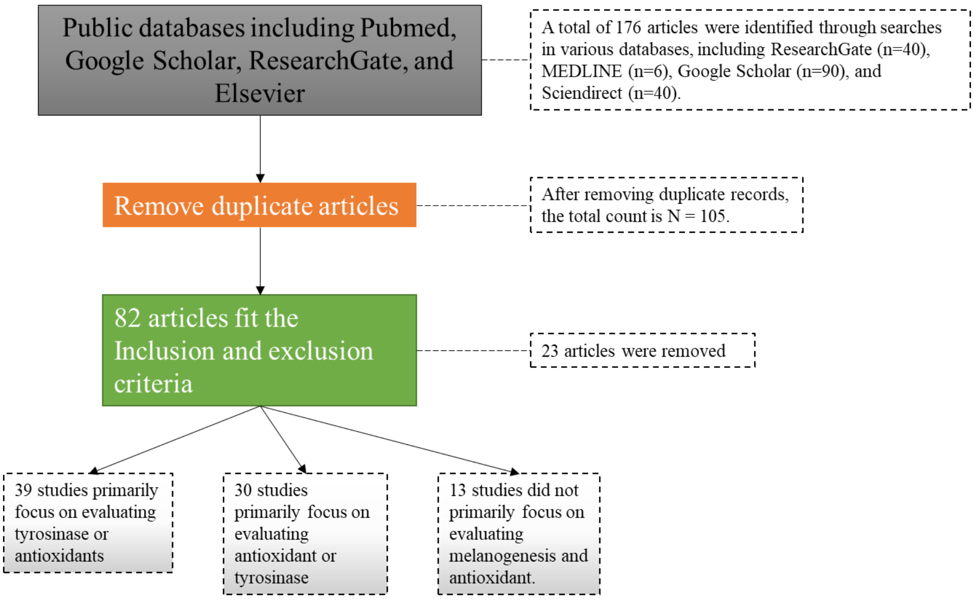

Figure 1. Study workflow

Brown seaweed has been consumed as food and used as medicine in Asian countries such Japan, China, and Korea. As traditional medicine, brown seaweed has been used for various treatments, such as kidney stone, stomach diseases, eczema, cancer, and kidney failure. Currently, seaweed is widely used in cosmetics. Research brown seaweed is aimed is developing new skin bleaching from marine (Resende *et al.*, 2021). Macroalgae has been reported to be used in skin-care products, which can act as skin softener, bleaching, UV protector (Thiyagarasaiyar *et al.*, 2021), and antioxidants, and has antibacterial, antifungal, anti-aging and anti-wrinkle properties (Namjooyan *et al.*, 2019). Latest review has focused on chemical compounds that have cosmetic potential from natural sources.

The main composition of brown seaweed are carbohydrates (mannitol, fucoidan, alginate, laminaran) (Rodriguez-Jasso *et al.*, 2011; Veide Vilg and Undeland, 2017), phlorotannins (unique polyphenols in brown seaweed), pigments, lipids, low molecular weight organics, proteins (Harrysson *et al.*, 2018) and some organic materials. It is common to extract alginate as a hydrocolloid from brown seaweed for widespread applications, particularly as gelling agents in cosmetics, pharmaceutical and food processing industries (Zhang *et al.*, 2020). Among diverse marine organisms, bacteria and algae are the largest source of active compounds. Brown, red and green algae each account for less than 59%, 40%, and 1%, respectively, from the global seaweed production (Agregán *et al.*, 2017)

METHODS

To initiate the research process, relevant information was sought by accessing various public databases including Pubmed, Google Scholar, ResearchGate, and Elsevier. The search was conducted using specific keywords to retrieve literature pertinent to the study, including "Fucoxanthin AND Antioxidant," "melanogenesis AND brown seaweed," "brown seaweed AND Tyrosinase," and "brown seaweed AND Cosmetic." Inclusion criteria were applied to select English language articles published up to May 2023, while exclusion criteria filtered out studies that did not sufficiently explain concepts related to antioxidant activity, melanogenesis, tyrosinase, and cosmetic applications of brown seaweed (Figure 1).

In this review, the assessment primarily focused on three key variables: antioxidant activity, tyrosinase inhibition, and the inhibition of melanin production in the cell line.

RESULTS AND DISCUSSION

The review revealed that out of the total studies analyzed, 39 specifically centered on assessing melanogenesis or tyrosinase inhibitors with antioxidant properties. Conversely, 30 studies primarily concentrated on investigating antioxidants or tyrosinase inhibitors. Furthermore, 13 studies did not predominantly focus on evaluating melanogenesis and antioxidants. (Supplementary Table I-III)

Seaweed, also known as marine macroalgae, holds immense promise as a renewable resource in the marine ecosystem. With over 6,000 identified species, seaweed is categorized into distinct classes: green seaweed (Chlorophyta), brown seaweed (Phaeophyta), and red seaweed (Benslima *et al.*, 2021). Among these, brown seaweed (Phaeophyceae) (Artemisia *et al.*, 2019) is particularly noteworthy for its rich content of bioactive compounds, including phlorotannin, phylopheophyllin, and the most prominent, fucoxanthin (Zhu *et al.*, 2023)

Fucoxanthin: Nature's Gift from the Sea

Fucoxanthin, a type of natural pigment that gives brown seaweed its brown to orange color, stands out as the dominant compound in the color composition. Together with other pigment such as chlorophyl, carotene, and xanthophyll (Sudhakar *et al.*, 2019). Beyond their aesthetic appeal, these pigments play crucial roles in supporting the biochemical processes essential for the life and growth of brown seaweed, exemplifying the beauty found in the diversity of natural compounds within marine ecosystems (Sreekala *et al.*, 2019). In addition, fucoxanthin not only has a significant role in natural carotenoid production, but also contributes more than 10% of the total estimated annual carotenoid production (Kotake-Nara and Nagao, 2011). Its presence in plants is not only limited to being a color pigment, but also shows its extraordinary functionality.

Moreover, fucoxanthin effectively functions as a photoprotective agent, helping to protect plants from damage caused by UV radiation and oxidative stress produced by exposure to sunlight. In addition, this compound is also involved in the upregulation of photosynthesis (Niu and Aisa, 2017), indicating its positive contribution in supporting essential biochemical processes that suppoty plant life. Thus, fucoxanthin is not only an aesthetic element, but also plays an important role in maintaining and improving plant health.

Chloroplasts are the place where chlorophyll-a, chlorophyll-c and apoprotein bind, forming permanent complexes that effectively capture light in the blue-green spectrum range. This complex then transfers energy into the photosynthetic electron transport cycle in algae. In addition, previous research (Nagao *et al.*, 2014) revealed that fucoxanthin has an important role in increasing photosynthetic efficiency by absorbing light inthe 449-540 nm range spectrum. Not only that, chlorophyll-a also takes part in the absorption of high intensity light in the 400-450 nm and 650-700 nm light spestrum. More interestingly, fucoxanthin and chlorophyll seem to complement each other in light absorption in plants, as has been revealed in previous studies (Jernelv, 2010). As additional information, macroalgae production, especially brown seaweed, can be obtained through organized cultivation or from wild brown seaweed populations (Pereira and Tavano, 2014).

Sources of Fucoxanthin

Fucoxanthin, a carotenoid pigment found in brown algae, absorbs more than 10% of total carotenoids and is reportedly a potent antioxidant based on various studies (Niu and Aisa, 2017). It also demonstrates tyrosinase inhibition activity, suggesting its potential as a skin-lightening agent (Shi *et al.*, 2022). Fucoxanthin, a carotenoid xanthophyll, is the dominant carotenoid in brown seaweed (Shi *et al.*, 2022). It is a highly abundant carotenoid, accounting for over 10% of the total estimated carotenoids in the marine environment (Chandini *et al.*, 2008). Interestingly, due to its complex chemical structure, fucoxanthin cannot be synthesized petrochemically.

Currently, commercially available fucoxanthin derived from seaweed is gaining significant economic value and potential for various applications (Yoshida *et al.*, 2023). The sustainability of this seaweed-based resource underscores its crucial role in developing sustainable and environmentally friendly alternatives in industry and research (Rosales-Mendoza *et al.*, 2020).

Fucoxanthin is a marine carotenoid with an interesting characteristic which gives brown seaweed yellowish or brownish color (Agregán *et al.*, 2017). Beyond its role as a pigment, fucoxanthin boasts notable medicinal benefits (Zhao *et al.*, 2017) and is derived from marine organisms, predominantly macro and microalgae(Méresse *et al.*, 2020). While brown macroalgae within the Phaeophyceae family are the primary natural source, the commercial industry focuses on microalgae cultivation to enhance fucoxanthin production (Gao *et al.*, 2020; Zhao *et al.*, 2022). Further, constituting approximately 10% of total carotenoids in nature, fucoxanthin is a xanthophyll pigment housed within the chloroplasts of brown seaweed (Petrushkina *et al.*, 2017). Its significance extends to the market, with the global carotenoid industry in food and cosmetics reaching a substantial value of US$ 120 million in 2022 (Lourenço-Lopes *et al.*, 2021).

Pharmacological Study

Fucoxanthin ($C_{42}H_{58}O_6$) stands as a phenolic compound stemming from the mevalonate and phenylpropanoid biosynthesis pathways, constituting the fundamental unit of isoprene, known as terpenes (Rajauria *et al.*, 2016; Seth *et al.*, 2021). A terpene that has forty carbon atoms is carotenoid. As a specific carotenoid found in diverse marine organisms such as brown seaweed, macroalgae, diatoms, and microalgae, fucoxanthin exhibits remarkable biological properties (Alghazwi *et al.*, 2019; Karpiński, 2019). Notably, fucoxanthin possesses a distinctive molecular structure characterized by an allenic bond and a 5,6-monoepoxide moiety (Ktari, 2021), with its detailed structure identified as 3′-acetoxy-5,6-epoxy-3,5′-dihydroxy-6′,7′-didehyro-5,6,7,8,5′,6′-hexahydro-β,β-carotene-8-one (Wang *et al.*, 2017, 2018, 2020) (Figure 2) (Zhao *et al.*, 2022).

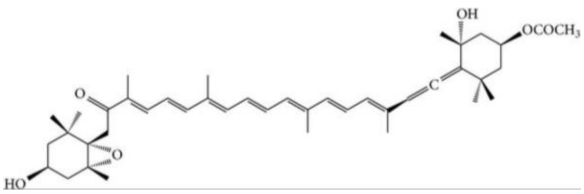

Figure 2. The molecular structure of fucoxanthin derived from brown seaweed.

Fucoxanthin is one of the most abundant carotenoids (Naveen *et al.*, 2021). Fucoxanthin has bioactivity that possesses protective role (Di Valentin *et al.*, 2012) including antioxidants, and anti-inflammation, for example anti-inflamation in colitis as dietary supplement (Liang *et al.*, 2023). It has anticancer (Wang *et al.*, 2019), anti-obesity, and anti-diabetic agents (Gager *et al.*, 2021), for example in combination with milk (Mok *et al.*, 2018). It also exhibits antiangiogenic, antimalaria, and hepatoprotective properties, and protects skin, brain, and eyes (Aditya, 2020; Miyashita *et al.*, 2020) . In addition, it has anti-microbial activities (Karpiński, 2019).

Fucoxanthin inhibits tyrosinase activity, melanogenesis in melanoma and UVB induced skin pigmentation (Agatonovic-Kustrin and Morton, 2018; Maeda *et al.*, 2018). The available scientific literature concerning the impact of fucoxanthin on melanogenesis is notably scarce. Although numerous studies have delved into extracts and fractions derived from brown algae, the specific discussion on fucoxanthin is lacking in this review.

Free Radical Quenching ability of Fucoxanthin

Research on natural compounds to identify antioxidants as molecules that are able to react with radicals or provide reducing power to fight oxidative stress caused by radicals. This approach is proven by several tests to test the the antioxidant activity of natural extracts or isolate compounds. Assay are carried out based on potential antioxidant reactions with several colored persistent radicals, for example DPPH or ABTS or using several non-radical oxidizing species such as Fe^{3+} (FRAP metal) (Liu *et al.*, 2021).

Antioxidant compounds are compounds that are able to slow down or inhibit the oxidation of materials that can be oxidized. Although it is used in very small amount (<1%, generally 1-1000mg/L) compared to the amount of compound that must be protected (Popović *et al.*, 2012). These compounds focus on biological system or organic molecules that make up tissues in both mammals and plants. Oxidation reactions occur through free radical chain reactions mediated by peroxide radicals (ROO) which are comparable to hydrocarbon antioxidants (Chandini *et al.*, 2008).

Antioxidant is a compound that can scavenge free radicals or reactive oxygen species (ROS) (Yang *et al.*, 2019). Antioxidants' ability as free radical scavengers is associated with its ability as a proton donor (Nurrochmad *et al.*, 2018). Various phenolic compounds can play a role as free radical scavengers with different capacity. The amount of hydrogen proton that is donated can be affected by the amount and aromatic of hydroxyl group and its position or hydroxyl from phenolic component (Rajauria, 2019). Free radicals are atoms or molecules that contain one or more unpaired electrons. To be stable, radicals need to donate electrons to other radical molecules. As a result of the reaction, donor molecules become new but unstable radicals, and they need electrons from surrounding molecules to be stable (Abdelhamid *et al.*, 2018).

Natural antioxidants are preferred to accommodate worldwide demand for antioxidants. A part from bioprospecting for natural and sustainable sources of antioxidants, many studies aim to investigate the bioactive relationship and antioxidant capacity of various natural materials such as algae as a producer of fucoxanthin (Burgos-Díaz *et al.,* 2022). Measurements of total carotenoids, phenolic acids, fucoxanthin content and fatty acid profiles are often carried out to support antioxidant assay (Foo *et al.*, 2017).

Natural antioxidants, including those found in macroalgae, play a vital role in defending against oxidative damage, a process triggered by abiotic stress that can lead to various tolerance and sensitivity reactions within species (Hashem *et al.*, 2021). Antioxidants act as protective agents, shielding the body from harm caused by free radicals, the harmful byproducts of oxidative stress (Shi *et al.*, 2022). This antioxidant capacity goes beyond mere biological stress response; it provides valuable insights into a species' ability to adapt and endure within its environment (Müller *et al.*, 2011). Understanding antioxidant capacity is crucial for deciphering physiological responses, and it holds immense value in unraveling the mechanisms of action and adaptation to oxidative stress (Urrea-Victoria *et al.*, 2022). Therefore, deepening our understanding of macroalgae's antioxidant capacity not only advances scientific knowledge but also opens doors to exploring its potential in developing strategies for environmental protection and human health (Chellappan *et al.*, 2020).

Natural antioxidants from plants are safer and can be used for alternative therapy (Motshakeri *et al.*, 2014). As a result, the demand for natural antioxidants is increasing (Foo *et al.*, 2017). Antioxidants are increasingly being used in food, drugs, and cosmetic products (Mourelle *et al.*, 2021) because of their role in protecting against damage from oxidative stress. Antioxidant screening is mostly done from plants (Gulcin, 2020). The results of antioxidant effect of brown seaweed extract that we obtained from several journal articles show various value depending on the seaweed species. Antioxidant power of an extract is determined by the compounds it has. A half of inhibition concentration (IC50) on the sample and different method show relatively the same value. Table 1 shows that brown seaweed was tested for its antioxidant using several methods, such as diphenylpicryl-hydrazyl (DPPH), ABTS, NO experiment and FRAP.

Fucoxanthin alters the molecular pathways associated with aging and is a present in mitochondria as source of ROS in cells (Guvatova *et al.*, 2020; NASER, 2021).

Fucoxanthin's Anti-melanogenesis Pathway

Melanogenesis is a process that consists of synthesis of melanin, transport of melanin, and release of melanosome (Kim *et al.*, 2018). Melanin is a compound which mainly determines colour of skin. Around 10% of cells in the deepest layer epidermis produce melanin pigment (Chan *et al.*, 2011). Melanin pigment is widely distributed in bacteria, fungi, plants, and animals and is produced through melanogenesis (Namjooyan *et al.*, 2019). In plants, melanin is useful for strengthening cell wall, does not contain nitrogen, and its color ranges from dark brown to totally black (d'Ischia *et al.*, 2015). The main role of melanin is to protect skin from damage coused by ultra violet. Melanin biosynthesis or melanogenesis is more widely known because of its physiological response that protects human skin against UV rays and other damage (Liu *et al.*, 2020). Melanogenesis is regulated by enzymes, such as tyrosinase, tyrosinase related protein-1 (TRP-1) and tyrosinase related protein-2 (Chan *et al.*, 2011).

Melanogenesis molecular process is determined by four core signal pathways. The first is the tyrosine kinase receptor (c-Kit receptor), activated by stem cell factor, mitogen activated protein (MAP activated) and followed by MIF. The second pathway is melanocortin-1 receptor (MC1R receptor) is activated by α-melanocyte-stimulating hormone (α-MSH) and ACTH, and interacts with c-AMP via identical adrenergic pathway. The third is adrenergic receptors bind noradrenalin and adrenalin that activate c-AMP bind, and followed by PKA and CREB. In the last pathway, nitrogen oxygen (NO) radicals activate guanylate cyclase that activates MIF and c-GMP. Specifically, Wnt receptor activates GSK3β (glycogen synthase kinase-3β) to promote phosphorylation and accelarate anti-melanogenesis. Phosphorylation inhibition in GSK3β increases catenins and complex LEF/TCA, and MIF is activated (Yang *et al.*, 2021). Activeted MIF promotes tyrosinase expression, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2) which is dopachrome tautomerase phosphorylation (DCT), and PKC-β, resulting in the formation of melanin. By contrast, in extracellular signaling, phosphorylation of MEK/ERK and P13K/AKT downregulates MIF, and anti-melanogenesis is leading. During phosphorylation, the phosphorylation process of MIF is activated (Lim *et al.*, 2016).

Fucoxanthin, as the dominant carotenoid in brown seaweed (Cui, 2020), is thought to be able to inhibit α-MSH, a hormone that stimulates melanin production. α-MSH binds to receptors on melanocytes, signaling them to produce melanin.

Table I. Antioxidant effect of brown seaweed

Species	Method	Outcome*	Reference
Sargassum macrocarpum extract	DPPH ABTS NO experiment, FRAP	6.746 mg ascorbic acid/g extract, 15,59 mg ascorbic acid/g extract 6.781 mg ascorbic acid/g extract 4.573 µg /1 gram extract	(Kim, 2021)
Turbenaria macroalgae	DPPH	IC = 8.33 mg/kg	(Wang *et al.*, 2018)
Turbenaria decurrens	BCB	63.73±4.09 µg/mL (extract) 57.07±2.45 µg/mL (fraction)	(Nurrochmad *et al.*, 2018)
	FRAP	161.67±3.22 mol/g extract 105.50±16.73 mol/g fraction	(Stranska-Zachariasova
	DPPH	316mg/g extract	*et al.*, 2017)
Laminaria digitata *Laminaria saccharina*		98.3 ± 2.78 µg/mL 222.4 ± 0.84 µg/mL	(Rajauria, 2019)
Himanthalia elongata (Phaeophyta)	DPPH	298.8 ± 5.81 µg/mL)	
Sargassun ilicifolium	DPPH, Reducing cooper ions	15.78 µg·mL^{-1} 11.19 µg·mL^{-1},	(Arguelles, 2021)
Vietnamese brown seaweed (*Padina australis*)	DPPH, FRAP	DPPH (1,417.01 mg TE/g FRAP (615.07 mg TE/g dry fraction)	(Hassan *et al.*, 2021)
Phlorotannin-Rich Fractions from Three Mediterranean Brown Seaweeds	DPPH, ABTS	(27.7 µg/mL) (19.1 µg/mL)	(Abdelhamid *et al.*, 2018)
Odontella aurita	DPPH ABTS	0,14 mg/mL 0,03 mg/mL	(Xia *et al.*, 2013)
Sargassum polycatum		8.75 ±1.10 mg AAE/g (aqueous extract) 1.24 ± 0.12 mg AAE/g(alcohol extract)	
Sargassum tennerium	DPPH	10.34± 1.35mg AAE/g(aqueous extract) 1.85±0.40 mg AAE/g (alcohol extract)	(Vasanthi *et al.*, 2020)
Sargassum cinctum		11.68±1.61mg AAE/g(aqueous extract) 1.47±0.37 mg AAE/g (alcohol extract)	
Bifurcaria bifurcata	DPPH	43.34 µg/mL	
	ORAC	1886.55±60.55 UmolTE/g	(Silva *et al.*,
	FRAP	95.83±4.48 µMFeSO$_4$/g extract	2019)

*The outcome serves as a parameter for IC$_{50}$ or EC$_{50}$.

By inhibiting α-MSH activity, fucoxanthin can help to reduce melanin production and lighten skin tone (Chen *et al.*, 2021). Fucoxanthin, the most abundant carotenoid in brown seaweed, plays a significant role in inhibiting melanogenesis, the process of melanin production in the skin (Bule *et al.*, 2018). This inhibition is thought to occur through multiple mechanisms, including suppressing the activity of α-MSH, a hormone that triggers melanin production, and interfering with the phosphorylation process, a crucial step in regulating various cellular pathways (Jang *et al.*, 2020). Consequently, fucoxanthin not only slows down melanin formation but also influences several cellular processes involved in this process (Slominski *et al.*, 2014).

Radical Scavenging Performance of Fucoxanthin

The antioxidant testing method (Table I) employs a range of techniques, including DPPH (1,1-diphenyl-2-picrylhydrazyl), ABTS (2,2'-azino-bis(3-ethylbenzothiazol-6-sulfonic acid)), NO (Nitric Oxide), FRAB (Ferric Reducing Ability of

Plasma), BCB (β-carotene Bleaching), and ORAC (Oxygen Radical Absorbance Capacity). Among these methods, the DPPH assay stands out as a particularly prominent one, frequently utilized for measuring antioxidant capacity (Sharma and Bhat, 2009; Tiwari *et al.*, 2021). The widespread preference for the DPPH assay can be attributed to its simplicity and ease of use compared to other antioxidant testing methods (Junopia *et al.*, 2020). Its ability to deliver relatively rapid and reliable results has made it a popular choice in antioxidant research. With the DPPH method (Rafi *et al.*, 2020), antioxidant capacity is evaluated by measuring the color change of the purple (Alam *et al.*, 2014). The utilization of the DPPH assay as the primary method for antioxidant testing (Table I) aligns with the principles of efficiency and accuracy in assessing the antioxidant potential of a substance or sample. Employing this method significantly contributes to the validity and interpretation of the antioxidant analysis results in this study.

Melanogenesis Inhibitory activity of Fucoxanthin

Melanogenesis is the process of melanin production that determines skin color. This coloring process is influenced by tyrosinase activity, melanogenesis in melanoma cells, and skin pigmentation caused by UV exposure. Additionally tyrosinase, a copper-containing enzyme, plays a pivotal role in the intricate process of melanin biosynthesis (Liu *et al.*, 2020). The conversion of L-tyrosine to L-DOPA and subsequently to dopachrome, catalyzed by the enzyme tyrosinase, is a key step in the melanin biosynthesis pathway (Schallreuter *et al.*, 2008). Dopachrome serves as the main precursor in the synthesis of melanin, the pigment responsible for skin and hair color (Zhou *et al.*, 2021). This process plays a critical role in protecting the skin from ultraviolet radiation and maintaining skin homeostasis (D'Mello *et al.*, 2016)

The significance of tyrosinase activity is particularly evident in melanocytes, specialized cells responsible for melanin production (Chan *et al.*, 2011). In melanoma cells, which are derived from melanocytes, tyrosinase activity is amplified, leading to uncontrolled melanin synthesis and the characteristic dark pigmentation associated with melanoma (Yang *et al.*, 2021). This process is an integral part of the regulation of cellular pigmentation, which in turn plays an important role in the function and biological response of the skin. Gaining a deeper understanding of tyrosinase enzyme activity could pave the way for targeted therapies or interventions addressing pigmentation disorders and melanoma-related conditions (Kumari *et al.*, 2018).

Several research studies have proven that brown seaweeds, *Sargassum polycystum*, *Undaria pinnatifida*, *Laminaria japonica*, and *Hizikia fosiformis,* inhibit the activity of melanin and the tyrosinase enzyme activities in melanoma cell. Researchers generally prefer to analyze extracts and fractions of fucoxanthin rather than pure isolates due to the challenges associated with isolation. The unstable nature of fucoxanthin makes it susceptible to degradation when exposed to heat and light, complicating the isolation process. Moreover, obtaining pure fucoxanthin for research samples can be prohibitively expensive (Table II).

Tyrosinase inhibitors are general approach to skin whitening because tyrosinase is a key enzyme in melanin biosynthesis (Chan *et al.*, 2011). Melanin biosynthesis pathway involves 2 different reactions. Hydroxylation of L-tyrosine catalyzes L-Dopa (monophenolase activity) and changes L-Dopa into dopaquinone by oxidation (dipheenolase activity)(Chan *et al.*, 2011). Tyrosinase is also responsible for browning in fruits, vegetables, reducing nutrition value, color damage, and sensors such as taste and texture. Tyrosinase inhibitors can be used in pharmacy and cosmetic industry as prevention and treatment (Arguelles and Sapin, 2020). Two main groups of compounds can inhibit tyrosinase enzyme activity: synthetic compounds and naturally occurring compounds, particularly those derived from plants (Kim *et al.*, 2014). While synthetic tyrosinase inhibitors are commonly used in cosmetics, concerns about their potential carcinogenic effects have sparked growing discussions about their safety (Jang *et al.*, 2020; Liu *et al.*, 2020). Driven by concerns about the safety of synthetic tyrosinase inhibitors, researchers are delving deeper into the exploration of natural alternatives, particularly those derived from plants. These natural compounds not only exhibit promising tyrosinase inhibitory potential but also hold the advantage of being generally considered safer and offering potential additional benefits for skin health (Wang *et al.*, 2020).

One promising natural compound gaining attention is brown seaweed. Beyond its richness in antioxidant carotenoids, brown seaweed has emerged as a potential tyrosinase inhibitor, prompting researchers to explore its active compounds and their interactions with the tyrosinase enzyme (Alghazwi *et al.*, 2019).

Table II. Anti-melanogenesis effect of brown algae

Species	Compound/Fraction/ Extract	Mechanism	Experimental system	Reference
Sargassum polycystum	Ethanolic extract & its hexane fraction	Inhibition of cellular TYR & melanin production	B16F10 Melanoma cells	(Chan *et al.*, 2011)
Undaria pinnatifida	Extract and fraction of ethyl acetate	Viability cell, melanin content, inhibition of mushroom TYR and melanin synthesis in B16F10 murine melanoma cells	B16F10 Melanoma cells	(Kim *et al.*, 2014)
Laminaria japonica	Fucoxanthin	Reducing TYR activity in B16F10 and melanin content in guinea pigs & mice skin, surpressing PGE2, MSH, TRP1& melanogenic stimulant receptors, NTR,EPI & MCIR	B16F10 Melanoma cells, UVB induced mice, & guinea pigs	(Azam *et al.*, 2017)
Hizikia fusiformis	4-hydroxyphenethyl alcohol	Inhibition of mushroom TYR and melanin synthesis in melanoma cell murin B16F10	B16F10 melanoma cells, brown guinen fraction	(Wang *et al.*, 2020)

Table III. Inhibitor effect (%) of brown seaweed at mushroom tyrosinase

No	Brown Seaweed	Method	Compound/Fraction/ Extract	Mushroom tyrosinase activity (%)	Reference
1	*Sargassum polycystum*	DPPH	Ethanolic crude extract	97.78±1.34	(Kim, 2021)
			Hexane fraction	97.10±0.55	
			Ethyl acetate fraction	100.58±1.81	
			Water fraction	99.49±0.73	
2	*Turbinaria decurrens*	BCB	Ethanolic crude extract	63.75±4.75 ug/mL	(Nurrochmad *et al.*, 2018)
			Chloroform fraction	57.75±0.44 ug/mL	
		FRAP	Ethanolic crude extract	161.67±3.22umol/g extract	
			Chloroform fraction	105.50±16.73umol/g extract	

Elucidating the potential of these natural compounds could pave the way for developing novel skin care ingredients that are not only effective in inhibiting melanin synthesis but also safe and sustainable (Niu *et al.*, 2018).

Fucoxanthin Anti-Melanogenesis Mechanism

Melanocytes are located on the basal layer of the skin that synthesizes melanin (Kumari *et al.*, 2018; Zhou *et al.*, 2021). Pheomelanin and eumelanin are produced in the melanosomes, a specialized organelle within melanocytes, through a series of reactions that are catalyzed by melanogenic enzymes (Alghazwi *et al.*, 2019). The synthetic pathways are divided into two roads: pheomelanogenesis and eumelanogenesis. Melanocyte transports the melanin pigments produced by melanosomes through their elongated dendrites into neighboring keratinocytes in the epidermis layer. Tyrosinase, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2), L-3,4-dihydroxyphenylalanine, and L-DOPA (Figure 3).

Tyrosinase inhibition (Figure 3) significantly impacts various stages of melanin synthesis. The reduced production of dopachrome, a consequence of tyrosinase inhibition, leads to decreased activity of the TRP-1 and TRP-2 enzymes.

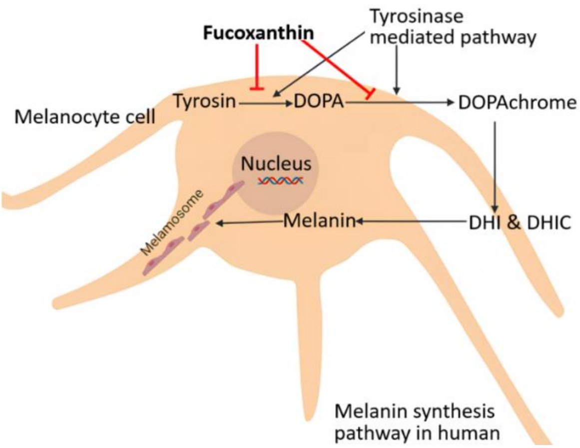

Figure 3. Fucoxanthin mechanism inhibition

This reduced activity, in turn, contributes to a decline in indole-5,6-quinone, a crucial compound in the melanogenesis pathway (Chen *et al.*, 2021). Consequently, the production of eumelanin, a type of melanin responsible for skin pigmentation, is diminished.

Moreover, the impact of eumelanin production on keratinocyte cells holds significant implications. Keratinocytes, the primary cells of the skin's epidermal layer, are the final destination of the produced melanin (Heo *et al.*, 2005). A reduction in eumelanin production can potentially influence overall skin pigmentation, ultimately affecting skin color and characteristics (Danimayostu *et al.*, 2023). Delving deeper into these mechanisms holds immense relevance for developing therapeutics or skincare products capable of selectively regulating them. This opens up the potential for treating various pigmentation disorders and developing more effective skincare formulations (Wang *et al.*, 2020).

Fucoxanthin plays a role in inhibiting tyrosinase activity, which results in a decrease in the production of compounds such as L-DOPA, TRP-1, TRP-2 and indole 5,6-Quinine. The impact of this inhibition is to reduce the process of melanin formation in the skin (Pintus *et al.*, 2015).

Future Perspectives of Fucoxanthin for Health and Beauty

Conventional cosmetic products tend to focus on the aesthetic aspect, while cosmeceuticals provide a holistic approach by including ingredients such as peptides, hyaluronic acid, retinol, vitamins and other antioxidants. The main advantage of cosmeceuticals lies in their ability to provide deeper health benefits, such as reducing pigmentation wrinkle, increasing skin moisture, or stimulating the regeneration of skin cells (Kurinjery and Kulanthaiyesu, 2022). The increasing interest in cosmeceuticals reflects a paradigm shift in consumer perceptions of beauty products. In addition to providing desired aesthetic results, cosmeceuticals in the cosmetic industry not only creates new trends, but also reflects (Lee and Nam, 2020; NASER, 2021).

Skin is considered a mirror of the body's health, therefore, preventing or treating skin problems is important. Algae, as one of the richest aquatic commodities, stands out as a healthful resource and has negligible impact on human cytotoxicity. The abundance of bioactive compounds in algae, such as vitamins, polyphenolic compound carotenoids. Chitin, and others, has consistently been reported to provide significant benefits for skin health (Malakar and Mohanty, 2021). Therefore, skin care products containing algae extract have been successfully commercialized, proving their effectiveness in treating various skin problems, including rashes, pigmentation, and signs of aging. Thus, utilizing the potential of algae as a skin care ingredient has become an approach that has been proven effevectine in maintaining healthy and beautiful skin (El-Chaghaby and Rashad, 2021).

Fucoxanthin is extracted from various sources, such as *Laminaria japonica*. It has been reported that this compound has an inhibitory effect on tyrosinase activity *in vivo* using guinea pigs as research model. Oral administration of fucoxanthin causes transcriptional sippression of melanogenesis factors because it inhibits the expression of skin mRNAs associated with the disease(Shimoda *et al.*, 2010)

Many research has been carried out regarding fucoxanthin as a cosmetics ingredient (Biskanaki *et al.*, 2023). One dosage form that has been developed is nanoparticles or nanformulations (Sharma *et al.*, 2023). The use of nanotechnology in this formulation aims to increase the bioavailability and effectiveness of fucoxanthin formulations show promise as an innovation in the cosmetics industry (Koyande *et al.*, 2021), opening up new potential to improve the penetratioan and performance of this ingredient in skin care product (Denis *et al.*, 2019).

The limitations of fucoxanthin in cosmetic development

Although Fucoxanthin shows potential as a whitening agent in cosmetics, there are several challenges to be addressed in its development. Fucoxanthin is susceptible to degradation when exposed to various factors such as light, heat, enzymes, oxygen, unsaturated lipids, and other prooxidant molecules (Rubba, 2009; Muradian *et al.*, 2015). This susceptibility limits its applications, particularly in industries such as pharmaceuticals and food, where stability is crucial for bioactive and colorant agents. Consequently, research efforts are focused on finding ways to stabilize Fucoxanthin and enhance its usability in cosmetic formulations, thereby maximizing its benefits in skincare products. Additionally, exploring innovative encapsulation techniques and storage conditions may offer solutions to mitigate its instability issues and unlock its full potential in cosmetic applications(Simal-gandara, 2023) . In addition, when considering development as an oral formulation, researchers must address the challenge of overcoming the low bioavailability of this compound. Furthermore, stability of this compound poses a significant challenge when scaling up to industrial levels. These factors necessitate comprehensive research into innovative delivery systems and formulation techniques to enhance the bioavailability and stability of Fucoxanthin, ensuring its efficacy and practicality in pharmaceutical applications (Sun *et al.*, 2018).

Currently, fucoxanthin represents a burgeoning sector primarily within the pharmaceutical and nutraceutical industries, with an emerging presence in the cosmetic sector. Despite its potential applications, there is a notable absence of research exploring fucoxanthin's utilization in animal feed beyond aquaculture contexts, where microalgae consumption is prevalent, or as a coloring agent in food or non-food products. Commercially, only a limited number of companies offer fucoxanthin-based products, typically in the form of algae biomass extracts or purified fucoxanthin extracts. Additionally, some products include the incorporation of polyunsaturated fatty acids to enhance their value. In the cosmetic industry, fucoxanthin serves as a complementary ingredient to existing cosmetic compounds available in the market, such as peptides, hyaluronic acid, retinol, and vitamins, augmenting their efficacy and broadening the scope of cosmetic formulations (Pajot *et al.*, 2022).

CONCLUSION

In conclusion, the utilization of fucoxanthin as a whitening agent holds significant promise owing to its antioxidative properties and ability to inhibit melanin production. Its dual functionality in combating oxidative stress and melanogenesis makes it an appealing choice for cosmetic formulations targeting skin whitening effects. Moreover, its natural derivation from brown seaweed, alongside its proven efficacy, positions fucoxanthin as a pivotal ingredient for cosmetic products addressing skin brightening and hyperpigmentation concerns. However, it's imperative to note that the handling of fucoxanthin requires careful consideration due to its stability challenges. Therefore, further research and development efforts are necessary to fully unlock the cosmetic potential of fucoxanthin and explore its versatile applications within the skincare industry.

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CONFLICT OF INTEREST

The author declares no conflict of interest

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