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Marine resources with melanogenic regulatory properties: seagrass, seaweed, and marine sponges as anti-melanogenic agents

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ABSTRACT

Tyrosinase is a rate-limiting enzyme that is essential for the synthesis of melanin and controls pigmentation in the skin. The most common strategy in cosmeceutical products for skin lightening is the suppression of tyrosinase. Marine substances contain a variety of unique chemical compounds that have the potential to develop into new bioactive compounds as future medications for skin hyperpigmentation therapy. In this review, we summarize 55 compounds from marine resources that have been identified as active in inhibiting tyrosinase enzyme activity from research studies published up to April 2023. Those substances are classified to be very strong, strong, and moderate inhibit tyrosinase activity and melanin biosynthesis. Based on the IC_{50} value, there are 12 compounds that act as potential anti-melanogenic agents. 7-phloroeckol isolated from *Ecklonia cava* has the highest tyrosinase enzyme inhibitory activity with an IC_{50} value of 0.85 µM, while Arenarol isolated from *Dysidea arenaria* has the most active properties in reducing the synthesis of melanin with an IC_{50} value of <3 µM on B16 melanoma cells. We propose to present a new perspective on the discovery of metabolites from seagrasses, seaweeds, and marine sponges that can be applied as lead compounds in developing medications for anti-hyperpigmentation therapy through this review.

INTRODUCTION

Melanin is a pigment that can be found in many kinds of species, including bacteria, fungi, plants, and mammals. The level and distribution of the melanin pigment determine a mammal's skin and hair color [1]. Melanin functions as a physical barrier to protect the skin from damage when it is exposed to UV radiation and reactive oxygen species (ROS) and contributes to identifying skin phenotypes [2]. For some people, discoloration of their skin caused by high levels of melanin pigment as a result of melanocyte activity induced by the tyrosinase enzyme might be an aesthetic and psychological issue [3]. Skin hyperpigmentation disorder is a description of this condition. The symptoms of skin hyperpigmentation disorders consist of lentigo, melanoma, melasma, and melanosis [4–7].

The treatment of skin hyperpigmentation may employ the administration of skin-lightening agents which act by either directly reducing the activity of the tyrosinase enzyme or by inhibiting the enzyme production process at the transcription or translation stage [8,9]. Tyrosinase, a copper-containing multifunctional metalloenzyme, is also known as polyphenol oxidase. The tyrosinase enzyme is crucial in the synthesis of melanin, due to the melanin biosynthesis pathway [3,4]. Tyrosinase works by catalyzing two initial stages in melanin formation, namely the monophenolase reaction, or hydrolyzing the change in the amino acid L-tyrosine to 3,4 dihydroxyphenylalanine (L-DOPA), and then the diphenolase reaction, or oxidizing L-DOPA to DOPAquinone [5,6].

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This approach can be used to remove dark spots on the skin brought on by hormone imbalance, post-inflammation, or UV radiation exposure [7]. The hydroquinone, arbutin, kojic acid, and ascorbic acid categories of lightening substances are some of those available on the market. Each of these substances has the ability to inhibit the synthesis of melanin [4,8,9]. However, the usage of skin-lightening agents may have many side effects, such as the permanent loss of melanocytes caused by hydroquinone when used continuously for an extensive period of time. Hereditary loss of skin color is caused by oxidative damage to lipid membranes, Which causes this disorder [10]. Due to those effects the use of hydroquinone was limited and has been replaced by arbutin and kojic acid, which appears to have no adverse effects on melanocyte cells [11,12]. Nevertheless, arbutin and kojic acid are known to have a lesser *in vivo* efficacy than hydroquinone, as well as adverse effects such as dermatitis, sensitivity, and erythema [13]. Other natural skin-lightening agents, such as ascorbic acid, tend to be thermolabile and easily broken down, thereby making them less stable when utilized [14]. Therefore, there is an urgent need for bioactive compounds that can inhibit the tyrosinase enzyme's activity as an anti-melanogenic agent.

Bioactive substances that have the ability to inhibit the tyrosinase enzyme, reduce the synthesis of melanin, and inhibit the expression of the tyrosinase gene have the potential to be developed as anti-melanogenic agents [15]. Compounds from the flavonoid, phenolic, and anthocyanin families are secondary metabolites that have activity as anti-melanogenic agents [16–18]. According to El-Nashar *et al.* [19], there are many distinct types of flavonoids in nature, including flavones, flavonols, isoflavones, flavan-3-ols, flavanones, and chalcones, which have tyrosinase inhibitory effects using diverse mechanism of action. Several derivatives of resveratrol such as oxyresveratrol and dihydrooxyresveratrol as potential depigmenting agents with IC_{50} values at 1.7 and 0.3 µM [20].

Natural materials with a variety of metabolites have unique chemical structures and various biological activities that can be found in marine natural resources. In accordance with their representation of 95% of the biosphere, marine resources give new opportunities for research on marine-derived medicines [21–23]. The complexity of marine ecosystems has prevented a thorough study of plants from watery ecosystems. Seagrass, seaweed, and marine sponges are several kinds of natural marine sources that have been investigated for bioactive substances. Marine macroalgae are a group of multicellular plant-like protists that are divided into three groups: brown algae (Phaeophyta), red algae (Rhodophyta), and green algae (Chlorophyta). The only angiosperm plant that flourishes in the marine environment is seagrass. Seagrass and seaweed are widely distributed in the waters of Southeast Asia and have many kinds of biological potential activities, such as antimicrobial, insecticidal, antimalarial, vasoprotective, anti-inflammatory, antioxidant, and anti-melanogenic properties [24–26]. In addition to seagrasses and macroalgae representing the kingdom plantae, and marine sponges representing the marine invertebrate phylum, also have the potential to be developed as anti-melanogenic agents. The existence of metabolites, such as pyrrole compounds, and peptides, which contribute to the inhibition of the tyrosinase enzyme, serves as evidence for this. According to several studies, pyrrole, and peptide compounds that have been identified from many kinds of natural sources have the ability to operate as tyrosinase inhibitors and can lower melanin levels in melanocyte cells [27–34].

The purpose of this review is to summarize the types of seagrasses, seaweeds, and marine sponges that possess anti-melanogenic activity *in vitro* and *in vivo*, to identify extracts, fractions, and compounds with potential activity based on IC_{50} values, and to reveal the most significant functions. An important category of bioactive compounds that have been shown to inhibit the activities of tyrosinase on various substrates. Nevertheless, additional *in vivo* study is required to support *in vitro* analysis and establish that bioactive substances effectively enhance the activity and selectivity of specific receptors in the test organism to act systemically. Therefore, it is possible to assess using either of these approaches that it has the potential to be developed specifically as an anti-melanogenic agent.

METHOD

Literature data about marine resources as an anti-melanogenic were extracted from the Scopus, PubMed, and Google Scholar databases. We browsed the database using the following keywords: "seagrass" OR "seaweed" OR "sponge" AND anti-melanogenic* OR "inhibitor tyrosinase" OR reduces melanin synthesis. The browsed scientific literature contained any of these keywords, terms, or phrases in their title, abstract, or keywords. The data included in this review were original articles or conference papers, the use of the English language only, and regarding the study of anti-melanogenic agents of compounds produced from seagrasses, seaweeds, and marine sponges, as shown in Table 1. Scientific literature with the following requirements was excluded, i.e., irrelevant terms, least, and biased information, unavailable full-text, and repetitions. The variables assessed in this review include seagrass species, seaweed species, sponge species, compounds of marine resources, experimental models, tyrosinase inhibition, inhibition of melanin synthesis, and cytotoxic effect.

Extraction and analysis of data

Figure 1 shows the data extraction and analysis of the research scope. The database's eligible literature was saved and evaluated further.

Anti-melanogenic activity of seagrasses

Seagrass is one group of aquatic plants that have not been thoroughly studied [35,36]. According to Reynold and Knowlton [37], seagrasses are marine plants that have roots and are capable of producing fruits and flowers (Angiosperms). The only flowering plants that can return to the seabed are seagrasses. Seagrasses also have an important role in supporting ecosystems for millions of marine organisms and helping stabilize sediments [37–39]. In the monocotyledon Alismatales, seagrasses are divided into four families: Cymodoceaceae, Hydrocharitaceae, Posidoniaceae, and Zosteraceae [38,40]. Seagrasses are marine vascular plants derived from higher land plants that later colonized marine habitats, but are often mistaken for algae. The majority of the basic and secondary

Table 1. Summarized data of antimelanogenic activity from seagrass, seaweed, and marine sponge.

No.	Species	Compound	Experimental models	IC_{50} (µg/ml)			Ref
				Tyrosinase inhibition	Inhibition of melanin synthesis	Cytotoxic effect	
			Seagrasses				
1.	*Syringodium isoetifolium*	Methanolic extract	Mushroom tyrosinase	25.92 mg/g	NT	NT	[35]
2.	*Posidonia oceanica*	Ethanolic extract	Mushroom tyrosinase	>1,000	NT	NT	[41]
			MeWo cells	NT	50	> 100	
3.	*Phyllospadix iwatensis*	Ethanolic extract (80%)	Mushroom tyrosinase	>1,000	NT	NT	[42]
			Melanoma B16 cells	NT	>300	Non toxic (>300)	
			HEM cells	600			
		Butanol fractionates	HEM cells	60			
		Luteolin 7-sulfate	Melanoma B16 cells	<3	>10	70	
			HEM cells	6	>10	60	
		Luteolin	Melanoma B16 cells	>10	>10	7	
			HEM cells	17	NT	60	
		Hispidulin 7-sulfate	Melanoma B16 cells	NT	NT	>100	
			HEM cells	>100	NT	>100	
		Hispidulin	Melanoma B16 cells	NT	NT	300	
			HEM cells	No inhibition at 100 µg/ml	NT	75	
			Seaweeds				
			Brown algae				
4.	*Fucus vesiculosus*	Fucoidan	Mushroom tyrosinase	11.5	NT	NT	[43]
			Melanoma B16 cells	NT	550		
5.	*Lobophora challengeriae*	Ethanolic extract	Mushroom tyrosinase	150	NT	NT	[44]
			Melanoma B16 cells	NT	>25	Non-toxic	
6.	*Laminaria japonica*	Fucoxanthin	Melanoma B16 cells	>15.1	>0.1%	NT	[45]
			Skin quinea pigs	NT	>0.1%	NT	
7.	*Sargassum polycystum*	Ethanolic extract	Mushroom tyrosinase	1,240	NT	NT	[44]
			Melanoma B16 cells	NT	NT	Non-toxic	
8.	*Sargassum ilicifolium*	Acidified methanol extract	Mushroom tyrosinase	125	NT	NT	[46]
9.	*Sargassum fuciforme*	Hijiki Liquor	3D Human skin models cells	51	NT	NT	[47]
		Methanol fractionation	3D Human skin models cells	3.1	>20,000	Non-toxic	
10.	*Sargassum angustifolium*	Methanolic extract	Mushroom tyrosinase	>500	NT	NT	[48]
11.	*Sargassum crassifolium*	Methanolic extract	Mushroom tyrosinase	>500	NT	NT	[48]
12.	*Sargassum glaucescens*	Methanolic extract	Mushroom tyrosinase	>500	NT	NT	[48]
13.	*Sargassum swartzii*	Methanolic extract	Mushroom tyrosinase	>500	>100	NT	[48]
			Zebrafish	>100	NT	NT	
14.	*Sargassum tenerrium*	Methanolic extract	Mushroom tyrosinase	>500	NT	NT	[48]

No.	Species	Compound	Experimental models	IC_{50} (µg/ml)			Ref
				Tyrosinase inhibition	Inhibition of melanin synthesis	Cytotoxic effect	
15.	*Sargassum silquastrum*	Aqueous extract	Mushroom tyrosinase	<100	72.68	Non-toxic	[49]
			Melanoma B16 cells	100	NT	NT	
			Zebrafish	NT	100 µg/ml	Non-toxic	
16.	*Sargassum plagyophyllum*	Methanolic extract	Mushroom tyrosinase	1,769.34	NT	NT	[50]
17.	*Padina australis*	Ethanolic extract	Mushroom tyrosinase	1,090	NT	NT	[44]
18.	*Padina boergesenii*	Methanolic extract	Mushroom tyrosinase	>100	NT	NT	[48]
			Zebrafish	<100	>100		
19.	*Padina distrimatica*	Methanolic extract	Mushroom tyrosinase	>500	NT	NT	[48]
20.	*Padina tetrastomatica*	Methanolic extract	Mushroom tyrosinase	>500	NT	NT	[48]
21.	*Padina minor*	Ethanolic extract	Mushroom tyrosinase	1,230	NT	NT	[44]
22.	*Turbinaria ornata*	Acidified methanol extract	Mushroom tyrosinase	67.50	NT	NT	[51]
23.	*Turbinalis conoides*	Ethanolic extract	Mushroom tyrosinase	4,620	NT	NT	[44]
24.	*Ecklonia cava*	Phloroglucinol	Melanoma B16 cells	Inactive	>250 µM	Non-toxic	[49,52,53]
		Eckol	Melanoma B16 cells	>100 µM	>250 µM	NT	
		Dieckol	Melanoma B16 cells	<100 µM	<250 µM	NT	
		7-phloroeckol	Melanoma B16 cells	0.85 µM	<250 µM	NT	
		Dioxinodehydroeckol	Melanoma B16 cells	222.94 µM	>100 µM	Non-toxic	
		Aqueous extract	Zebrafish	>100	>100 µg/ml	Non-toxic	
25.	*Ecklonia stolonifer*	Phloroglucinol	Mushroom tyrosinase	92.8	NT	NT	[54]
		Eckstolonol	Mushroom tyrosinase	126	NT	NT	
		Eckol	Mushroom tyrosinase	33.2	NT	NT	
		Phlorofucofuroeckol	Mushroom tyrosinase	177	NT	NT	
		Dieckol	Mushroom tyrosinase	2.16	NT	NT	
26.	*Eisenia bicyclis*	PFF-A	Melanoma B16 cells	Inactive	50	Non-toxic	[55]
27.		FF-A	Melanoma B16 cells	Inactive	50	Non-toxic	[55]
28.	*Ishige okamurae*	Methanolic extract	Mushroom tyrosinase	<100	NT	NT	[56]
		Ethyl acetate fraction	Melanoma B16 cells	<100	NT	NT	
		Diphlorethohydroxycarmalol (DPHC)	Melanoma B16 cells	142.20 µM	32.72 µM	NT	
29.	*Myagropsis myagroides*	Sargachromanol G	Mushroom tyrosinase	>5,000	NT	NT	[57]
		Sargachromanol I	Mushroom tyrosinase	>5,000	NT	NT	
		Mojabanchromanol b	Mushroom tyrosinase	>5,000	NT	NT	
30.	*Cladosiphon okamuranus*	Hexane/dichloromethane extract	Mushroom tyrosinase	<1,000	NT	NT	[47]
31.	*Colpomenia sinuosa*	Methanolic extract	Mushroom tyrosinase	>500	>100	NT	[48]
			Melanoma B16 cells	>100	NT	NT	

No.	Species	Compound	Experimental models	IC_{50} (µg/ml)			Ref
				Tyrosinase inhibition	Inhibition of melanin synthesis	Cytotoxic effect	
32.	*Cystoseira trinodis*	Methanolic extract	Melanoma B16 cells	>500	NT	NT	[48]
33.	*Endarachne binghamiae*	Aqueous extract	Mushroom tyrosinase	<100	NT	NT	[49]
34.	*Schizymenia dubyi*	Aqueous extract	Mushroom tyrosinase	<100	NT	NT	[49]
			Red algae				
35.	*Gracilaria fergusonii*	Methanolic extract	Mushroom tyrosinase	3,730	NT	NT	[58]
36.	*Gracilaria verrucosa*	Aqueous extract	Mushroom tyrosinase	>100	NT	NT	[49]
37.	*Eucheuma cotonii*	Methanolic extract	Mushroom tyrosinase	2,631.65	NT	NT	[50]
38.	*Gelidium amansii*	Aqueous extract	Mushroom tyrosinase	<100	NT	NT	[49]
39.	*Spyridia hypnoides*	Methanolic extract	Mushroom tyrosinase	3,700	NT	NT	[58]
40.	*Amphiroa anceps*	Methanolic extract	Mushroom tyrosinase	4,490	NT	NT	[58]
			Green algae				
41.	*Caulerpa lentillifera*	Ethanolic extract	Mushroom tyrosinase	>5,000	NT	NT	[44]
42.	*Caulerpa racemosa*	Ethanolic extract	Mushroom tyrosinase	>5,000	>25		[44]
43.	*Ulva intestinalis*	Ethanolic extract	Mushroom tyrosinase	3,350	NT	NT	[44]
			Melanoma B16 cells	NT	>25	Non-toxic	
44.	*Ulva conglobata*	Aqueous extract	Mushroom tyrosinase	>100	NT	NT	[49]
45.	*Ulva pertusa*	Aqueous extract	Mushroom tyrosinase	>100	NT	NT	[49]
46.	*Halimeda spp.*	Methanolic extract	Mushroom tyrosinase	3,070	NT	NT	[58]
47.	*Valoniopsis pachynema*	Methanolic extract	Mushroom tyrosinase	3,680	NT	NT	[58]
48.	*Codium contractum*	Aqueous extract	Mushroom tyrosinase	>100	NT	NT	[49]
49.	*Enteromorpha compressa*	Aqueous extract	Mushroom tyrosinase	>100	NT	NT	[49]
50.	*Monostroma nitidum*	Aqueous extract	Mushroom tyrosinase	>100	NT	NT	[49]
			Marine Sponge				
51.	*Phorbas sp.*	Gagunin D	Mouse Melan-a cells	>20 µM	12.7 µM	Non-toxic	[27]
52.	*Geodia japonica*	Geoditin A	Melanoma B16 cells	1	≤5	Non-toxic	[28]
53.	*Haliclona sp.*	Dichloromethane extract	Mushroom tyrosinase	<100	NT	NT	[59]
54.	*Dysidea arenaria*	Arenarol	Melanoma B16	< 3 µM	< 3 µM	Non-toxic	[60]
			NHMs	> 3 µM	> 3 µM	Non-toxic	
55.	*Halichondria moorei*	HTS	Melanoma MM418	>50	>100	Non-toxic	[61]

NT: Not tested.

metabolic characteristics of seagrasses and their relatives Alismatales that inhabit terrestrial and freshwater habitats are very identical [39,62].

Coastal communities use seagrass biomass as food and for medicinal purposes, such as the treatment of fever, skin diseases, muscles, wounds, stomach aches, anti-pain against stingray stings, and as a potential antimicrobial agent [63]. The fishing communities in the Cuddalore and Nagapattinam areas of Tamil Nadu, South India, employ this *Halophila ovalis* as a medication to cure various skin conditions, burns, and ulcers [64]. According to Yuvaraj *et al.* [65], it is also employed as a potent anti-inflammatory and antioxidant. In the Philippines, the seeds of the tropical seagrass *Enhalus acoroides* are traditionally consumed [66] and are considered to have aphrodisiac and contraceptive properties [67]. *Enhalus acoroides* has a number of interesting biological activities, including antibacterial, insecticidal, antimalarial, vasoprotective, anti-inflammatory, antioxidant, and antialgal characteristics [24]. However, as far as we can tell from our examination of the literature, there has not been a review that discusses the anti-melanogenic properties of seagrass.

Presently, research on the anti-melanogenesis activities of seagrass metabolites has been relatively limited when compared to seaweeds. Based on a review of the literature published up to April 2023, we include three original articles for review (Table 1). Three species whose anti-melanogenic

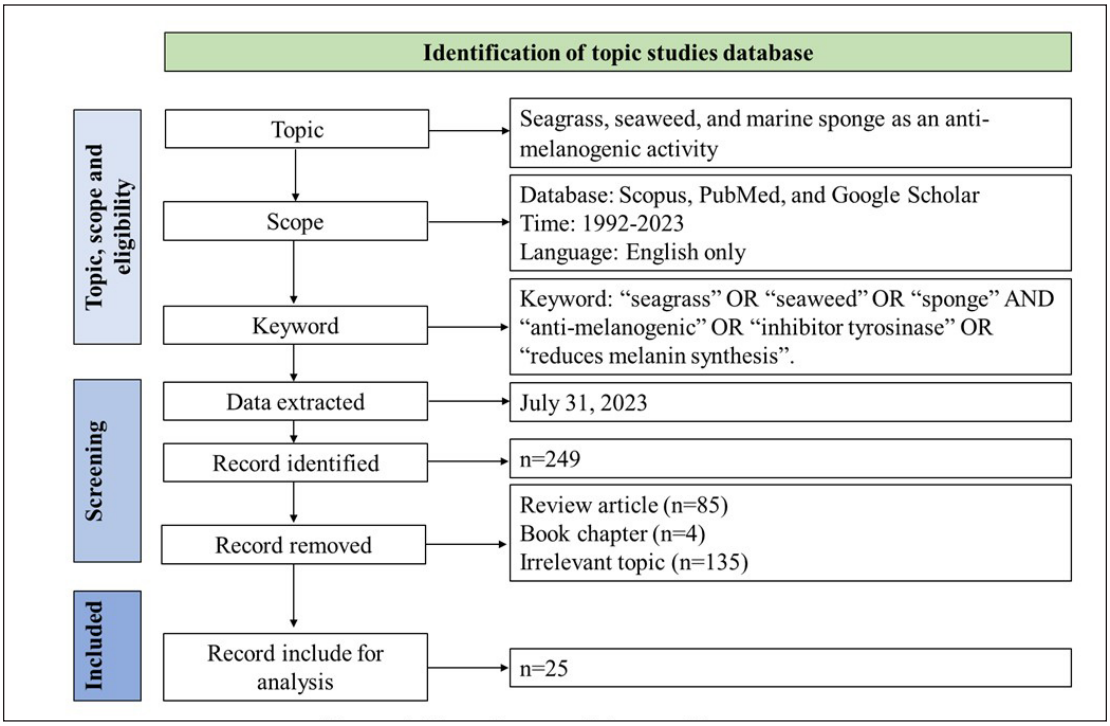

Figure 1. Flow diagram of the searching strategy.

properties have been studied such as *Syringodium isoetifolium*, *Posidonia oceanica*, and *Phyllospadix iwatesis*. A limited amount of bioactive substances have been identified from seagrasses that are known to inhibit the tyrosinase activity, including caftartic acid, loliolide, and iso loliolide from *S. isoetifolium* and luteolin 7-sulfate from *Phyllospadix iwatensis*. Caftartic acid, loliolide, and iso loliolide were able to bind to the active site of the tyrosinase enzyme by *in silico* study, while *S. isoetifolium* methanol extract had an IC_{50} value of 25.92 mg/g when tested *in vitro* for tyrosinase inhibitory activity [35]. Strong anti-melanogenic activity against murine melanoma B16 cells and human epidermal melanocytes (HEM) is exhibited by luteolin 7-sulfate, which was extracted from the butanol extract of *P. iwatensis,* without accompanied adverse effects were observed on B16 and HEM cells [42]. The melanin content could be decreased by the ethanol extract of *P. oceanica* with an IC_{50} value of 50 µg/ml; however, the toxicity effect on MeWo cells was shown with an IC_{50} >100 g/ml [41]. Based on these findings, the further investigation is needed for the development of skin-lightening agents, and there are still several potentials to use seagrass as a research subject, considering that there is still an abundance of scientific knowledge on the subject.

Anti-melanogenic activity of seaweed

Compounds of natural products from marine algae have been well investigated and examined. Algae are eukaryotic photosynthetic organisms that can adapt to diverse environmental situations by generating a variety of secondary metabolites and bioactive constituents, containing phlorotannins and polysaccharides [68,49,56,52]. Numerous studies have been conducted on the functions of bioactive substances and secondary metabolites. These substances exhibit anti-oxidant, anti-inflammatory, anti-melanogenic, anti-proliferative, and anti-aging properties [69–72]. However, limited studies have been conducted to examine the interaction between this compound's biological activity as a skin-lightening agent and its effectiveness as a depigmenting agent. Three types of marine algae are classified as brown (Phaeophyta), red (Rhodophyta), and green (Chlorophyta). Due to their capacity to adapt to numerous and challenging environmental conditions, these three categories of algae exhibit a wide range of biological activities and are well known for producing several types of bioactive chemicals, including polysaccharides, carotenoids, and flavonoids [73,74]. These bioactive compounds were studied, and it was shown that they had anti-oxidant, anti-inflammatory, photo-protective, and anti-melanogenic activities [15,70,72,75,76]. As a target for skin lightening, this kind of biological activity can be exploited.

In comparison to seagrass, seaweed metabolites are the subject of substantially greater study at the moment. A literature review through April 2023 led to the inclusion of 17 original publications for review (Table 1). We examined 26 different genera that are known to have anti-melanogenic effects and discovered that most research was done on the brown algae genus Sargassum. Although many of these bioactive substances have been found in seaweed [49,56,52,43,45,53,54,57], research on the anti-melanogenic properties of these compounds is still limited.

Anti-melanogenic activity of sponges

Due to reveals, marine sponges are exceptional in terms of identifying active metabolites with the potential to be utilized in medicines. An invertebrate species from the

phylum Porifera known as a marine sponge has a sessile way of life, has porous bodies, and collects small particles of food from seawater. They produce metabolites as a form of defense to protect themselves from predators and fouling organisms that tend to attach to their outside surface. Sponges are a major marine resource to produces several types of distinctive and varied bioactive metabolites, as has been explained during the past 30 years. Sponge species consisting of more than 8,000 have been reported and have a wide distribution in the marine environment [77,78]. Due to the many different chemical and physical conditions, nearly every group of marine sponges produces a variety of bioactive compounds with unique structural properties [79,80]. Natural compounds derived from marine sponges have the potential to offer a promising novel treatment option for skin hyperpigmentation disorders [28,61,60]. Bioactive compounds synthesized by marine sponges are chemically diverse and can be grouped as nucleosides, terpenes, sterols, cyclic peptides, and alkaloids [81]. These substances have a strong potential for antioxidant activity, according to previous research. Following the results of previous studies, a compound with antioxidant activity can reduce hyperpigmentation by using a ROS scavenger [82–84].

Existing natural products have been used as lead compounds in the synthesis of derivative compounds having more potential to develop as pharmaceutical medicines [85]. Presently, research on the anti-melanogenesis activities of marine sponge metabolites has been relatively limited when compared to antioxidants, antibacterials, and anticancer activity. Based on a review of the literature published up to April 2023, we include five original articles for review (Table 1). We studied five different genera that have been studied for their anti-melanogenic properties and it has been possible to isolate each of its bioactive ingredients. Even though various bioactive substances from marine sources have been found [27,61,60,28,59], the traceability of their anti-melanogenic activity is still limited.

Figure 2 shows the studies that have been conducted on the anti-melanogenic properties of marine resources such as seagrass, seaweed, and marine sponges, with the number of publications increasing every year. Four article publications made up the majority of those that were released in 2020, with three publications coming in 2019 and 2021. From 1992 until 2018, the number of publications varied and then increased after that year. There are limited studies on anti-melanogenic activity because researchers are more interested in other activities such as antimicrobial, antitumor, and anticancer. They are also interested in chemical compounds produced by symbiotic relationships between sponges and microorganisms. Seaweed metabolites have been established in numerous studies evaluating anti-melanogenic seaweed metabolites to have inhibitory activity against the tyrosinase enzyme and to be able to reduce melanin content in cells. It is also possible to extract prospective metabolites that may eventually be developed as anti-hyperpigmentation therapeutics if further research is conducted, especially from seagrass and sponge materials.

Classification of anti-melanogenic activity of compounds from seagrasses, seaweed, and sponges

In this review, we list the bioactive compounds that have recently been discovered in seagrasses, seaweeds, and marine sponges that have been shown to have anti-melanogenic properties. The units are converted to the same units, or g/ml, to compare IC_{50} results. Moon *et al*. [86] defined the classification of all components based on the IC_{50} value, classifying the activity of the tyrosinase inhibitor component as "very potent inhibitory": IC_{50} 10 g/ml, "strong inhibitory": IC_{50} is 10–100 g/ml, and "moderately inhibitory": IC_{50} is 100–500 g/ml. Tyrosinase inhibitors, inhibition of melanin synthesis in cells, and nontoxicity to melanocyte cells are among the characteristics

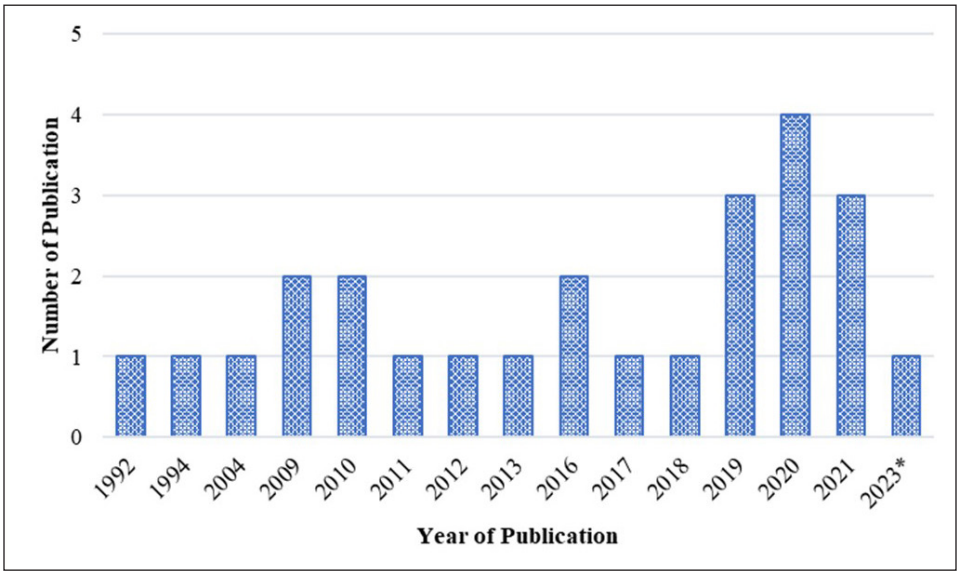

Figure 2. Distribution of conducted studies about seagrasses, seaweeds, and marine sponges metabolite exploration for anti-melanogenic activity.

that can be tested to assess a component's anti-melanogenic activity. The types of test cells used in this study differ in their ability to inhibit the activity of the melanin content, thus it is possible that various IC_{50} values represent components that are inactive in different test cell melanocyte types. Reviewing the efficacy of inactive substances derived from seagrass, seaweed, and sponges may represent an excellent concept.

In this study to determine the inhibition of tyrosinase, five different types of melanocyte cells, whether in melanoma or normal conditions, were used. Murine melanoma B16, HEM, mouse Melan-a, normal human melanocyte (NHM), and melanoma MM418 are the most common types of skin melanocyte cells, which cell models have relevance for the assessment of the anti-melanogenic substance. To investigate new compounds derived from marine resources such as seagrass, seaweed, and marine sponges, many researchers have focused their study on these five types of cells. Potential marine resource compounds are anticipated to be utilized as new drugs for the treatment of hyperpigmentation disorders. Researchers utilized an *in vitro* study with a cell line and the tyrosine enzyme to facilitate the screening of the anti-melanogenic activity of components obtained from marine resources. In this study, we identified five different types of melanocyte cell lines that were utilized to assess the anti-melanogenic activity of substances derived from marine sources. The use of this tyrosine enzyme and melanocyte cells were also taken into account by other considerations. These characteristics include easy handling and alteration, ideal homogeneity, a high degree of representation of the initial subject, a limitless auto-replicative source, and the ability to reproduce effects given the right conditions. In addition, normal melanocyte cells are also utilized.

Tables 2 and 3 and Figures 3 and 4 show the marine resource-isolated substances classified as very strong and strong tyrosinase inhibitors and synthesis of melanin inhibitors. The flavone or flavonoid luteolin 7-sulfate and luteolin have a yellow crystalline appearance. It is found in a wide variety of plant species, including celery, carrots, olive oil, peppers, and various species of marine macroalga. According to López-Lázaro [87], this metabolite exhibits a variety of biological properties, including antioxidant, anti-inflammatory, antibacterial, and anticancer properties. Phloroglucinol, 7-phloroeckol, dioxinodehydroeckol, phlorofucofuroeckol, eckol, and dieckol are examples of bioactive phlorotannin derivatives that have been identified in the edible brown algae arame (*Ecklonia bicyclis*) and turuarame (*Ecklonia stolonifera*) [88]. Tyrosinase inhibitory properties of phlorotanin derivatives present the possibility of being developed as depigmenting agents [52,54,89].

Table 2. List of compounds with very strong and strong tyrosinase inhibitor activity based on the IC_{50} value.

No.	Compounds	Inhibition category	Experimental model
1.	Luteolin 7-sulfate	Very strong	Melanoma B16 and HEM cells
2.	Luteolin	Strong	Melanoma B16 and HEM cells
3.	Fucoidan	Strong	Mushroom tyrosinase
4.	Fucoxanthin	Strong	Melanoma B16 cells
5.	Eckol	Strong	Mushroom tyrosinase
6.	Dieckol	Strong	Melanoma B16 cells
7.	Phloroglucinol	Strong	Mushroom tyrosinase
8.	7-phloroeckol	Very strong	Melanoma B16 cells
9.	Gagunin D	Very strong	Mouse Melan-a cells
10.	Arenarol	Very strong	Melanoma B16 cells and NHMs
11.	Geoditin A	Very strong	Melanoma B16 cells
12.	HTS	Strong	Melanoma MM418 cells

Table 3. List of compounds with very strong and strong biosynthesis melanin inhibitor activity based on the IC_{50} value.

No.	Compounds	Inhibition category	Experimental model
1.	Luteolin 7-sulfate	Strong	Melanoma B16 and HEM cells
2.	Luteolin	Strong	Melanoma B16
3.	Fucoxanthin	Very strong	Melanoma B16 cells
4.	Gagunin D	Very strong	Mouse Melan-a cells
5.	Arenarol	Very strong	Melanoma B16 cells
6.	Geoditin A	Very strong	Melanoma B16 cells

Functional group in potent anti-melanogenic activity

Luteolin and luteolin 7-sulfate (Fig. 5) is a pure yellow crystalline powder representing the category of bioflavonoid. Luteolin is present in many different types of plants, while the luteolin 7-sulfate is only present in a few species of plants, such as *P. iwatensis* Makino and *Zotera marina*, a marine algae [90,91]. In a previous study, luteolin 7-sulfate isolated from *P. iwatensis* was shown to inhibit cellular melanin synthesis. The cAMP-responsive element binding protein and microphthalmia-associated transcription factor (MITF)-mediated signaling pathways are involved in the mechanism of action of luteolin 7-sulfate, which reduces melanin synthesis by weakening the expression of the TYR gene [34,92].

Fucoidan and fucoxanthin (Fig. 5) are two compounds extracted from brown seaweed. *Fucus vesiculosus*, *Cladosiphon okamuranus*, *Laminaria japonica*, *Sargassum fusiforme,* and *Undaria pinnatifida* are examples of brown algae that produce fucoidan and fucoxanthin [93]. Both fucoidan and fucoxanthin show anti-melanogenic properties. Fucoidan occurs in the cell walls of brown seaweed, protecting seaweeds from external stress, while fucoxanthin is the pigment responsible for the olive-green color of brown seaweeds. Moreover, the main of fucoxanthin is to harvest light as a part of the process of photosynthesis. Fucoxanthin inhibited tyrosinase activity, melanogenesis in melanoma, and UV-B-induced skin pigmentation. Topical application of fucoxanthin (1%) significantly suppressed mRNA expression of tyrosinase-related protein 1 [45].

Phlorotannins, representing about 5%–12% of the dry mass of marine brown algae (Phaeophyta), are polyphenolic chemicals based on phloroglucinol (13,5-trihydroxy benzene). Phloroglucinol oligomers have been polymerized by polyketides

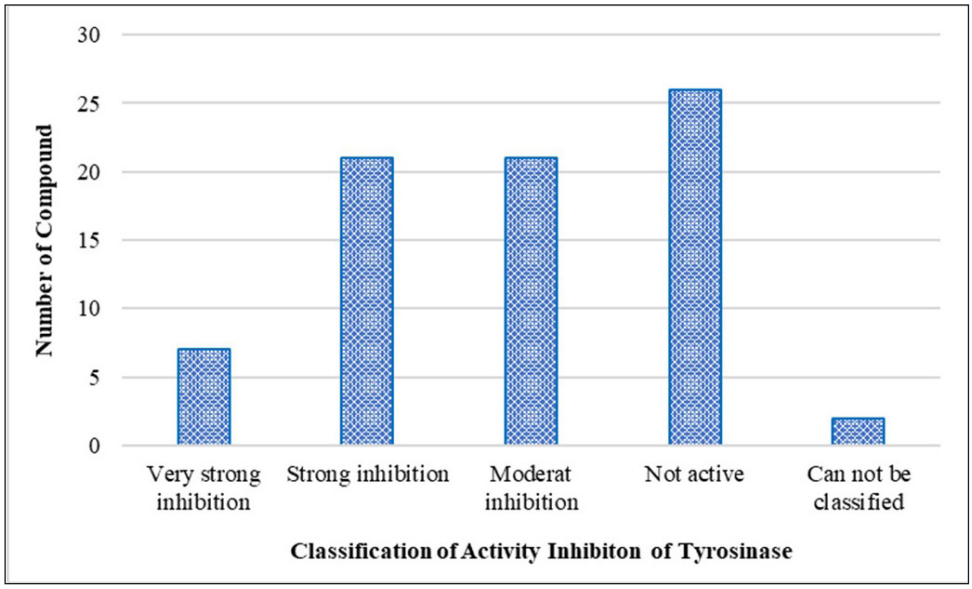

Figure 3. Classification of compounds with tyrosinase inhibitory activity based on IC50 values.

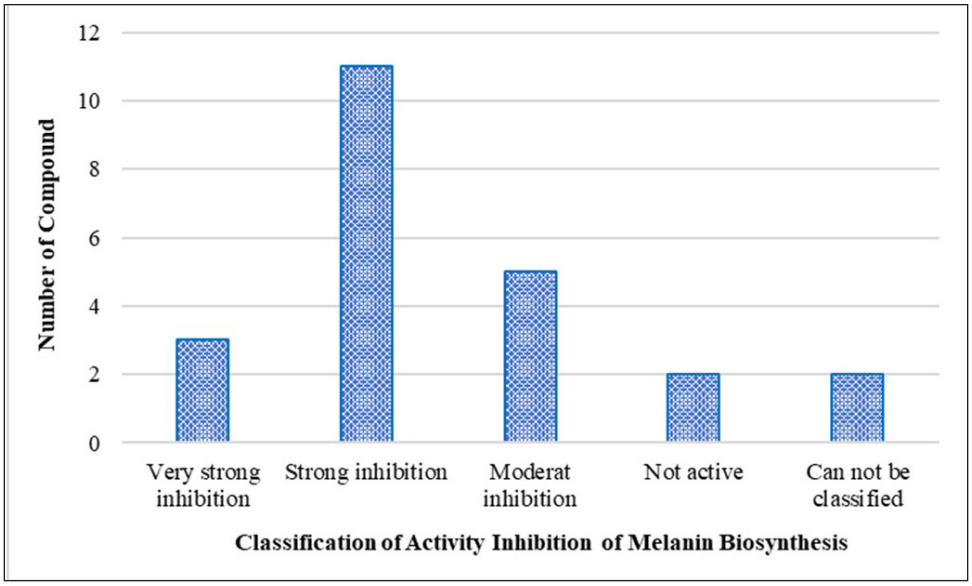

Figure 4. Classification of compounds with biosynthesis melanin inhibitory activity based on IC50 values.

(acetate-malonate) to produce phlorotannins. Phlorotannins with biological activity that support health have been found in several species of marine brown algae, including *Hizikia fusiformis*, *Ecklonia cava*, *L. japonica*, *Ecklonia kurome*, *Ishige okamurae*, *Sargassum thunbergii*, *E. bicyclis*, *U. pinnatifida*, and *E. stolonifera* [94]. Phlorotannins have been found to inhibit tyrosinase, an essential enzyme for the production of melanin. Two phlorotannins, phlorofucofuroeckol-A (PFF-A), and fucofuroeckol-A (FF-A), from the *E. bicyclis* were recently shown to reduce the biosynthesis of melanin in mouse B16 melanoma cells [55]. The downregulation of TYR and transcription factors associated with microphthalmia by FF-A inhibits melanin production. These results suggest that phlorotannin might regulate melanin to be important for treating hyperpigmentation disorders.

Gagunin D (Fig. 5), a highly oxygenated diterpenoid which is isolated from marine sponge *Phorbas* sp., has significantly inhibited tyrosinase enzyme activity and decreased the melanin content the melanin without cytotoxicity effect on Melan-a cells at 20 µM for 72 hours. Gagunin D also effectively downregulated the protein level of MITF at 20 µM [27]. Geoditin A an isomalabaricane triterpene which is isolated from the marine sponge *Geodia japonica*, has significantly inhibited tyrosinase enzyme activity and decreased the melanin content the melanin without cytotoxicity effect on murine melanoma B16 cells at 1 µg/ml. Contribute Geoditin A to melanogenic inhibition

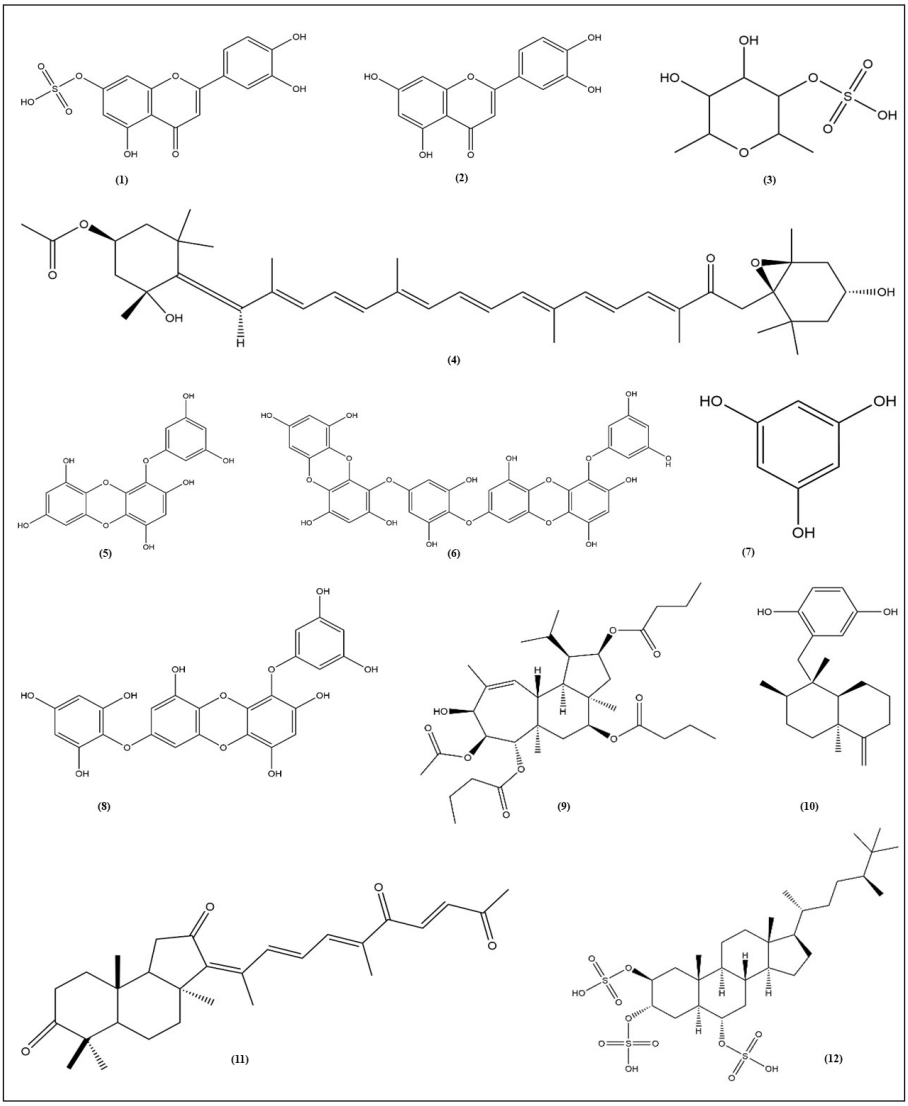

Figure 5. Structure of anti-melanogenic compounds. Luteolin 7-sulfate (1). Luteolin (2). Fucoidan (3). Fucoxanthin (4). Eckol (5). Dieckol (6). Phloroglucinol (7). 7-phloroeckol (8). Gagunin D (9). Arenarol (10). Geoditin A (11) HTS (12).

was mediated through modulation of the cAMP pathway [28]. Osirisyne derivates are polyacetylenes that are widely distributed in marine sponge *Haliclona* sp. Dichloromethane extract containing osirisyne derivates has presented significant anti-tyrosinase activity with % inhibition up to 68.9% at 100 µg/ml [59]. Halistanol trisulphate (HTS) caused immediate inhibition of synthesis melanin at 100 µg/ml after 24 hours of treatment. HTS inhibits the maturation of tyrosinase to a form associated with melanin synthesis [61]. Arenarol is a sesquiterpenoids with rearranged drimane skeletons from marine sponge *Dysidea arenaria*. This compound is potential to be developed into anti-pigmented effect. Inhibitory effect of arenarol on TYR activity at 3.0 µM without cytotoxic after 3 days post-treatment [60].

CONCLUSION

The review's data showed that the metabolites produced from marine natural resources have the potential to be used as a regulator of melanin biosynthesis. Based on the components that have been summarized, the promising components to be developed as depigmenting agents are derivatives of flavonoids, polysaccharides, and phlorotannin isolated from seaweed, terpenoid derivatives isolated from sponges, while metabolites sourced from seagrass need further exploration because the information about bioactive compounds that have the potential to perform the role of tyrosinase inhibitors is currently very limited. To evaluate the specific mechanism of action of the bioactive components as anti-melanogenic substances, a thorough approach is needed.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve the use of animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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