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Review Article

A REVIEW OF MARINE NATURAL PRODUCTS AS POTENTIAL SOURCE OF ANTIOXIDANTS

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ARTICLE HIGLIGHTS

- Marine Natural Products have been the most favorable source of bioactive compounds for drug discovery research.
- Many biologically active chemicals with antioxidant properties can be found in the marine environment.
- A systematic review on potential source of antioxidants linked to marine natural products was carried out.
- Algae, fungi, sponges, mollusks, and sea cucumbers were found to be abundant sources of antioxidants.
- Integrate these discoveries into practical applications for enhancing human health and well-being.

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ABSTRACT

Several diseases have been linked to oxidative stress, resulting from an imbalance between the creation of the body's antioxidant defense mechanisms and reactive oxygen species (ROS). Due to their distinct metabolic makeup and wide range of biological adaptations, marine organisms have attracted interest as possible sources of new antioxidants. This systematic review aims to evaluate the antioxidant potential of marine natural products. To find relevant research published between 2002 and 2022, a thorough search strategy based on the PRISMA standards was used across databases, including PubMed, Google Scholar, Mendeley, and Science Direct. A total of 18 studies were extracted and included in the review. The results consistently showed that marine natural compounds had vigorous antioxidant activity. Algae, fungi, sponges, mollusks, and sea cucumbers were shown to be abundant sources of antioxidants in marine environments. Flavonoids, alkaloids, phenols, tannins, steroids, saponins, glycosides, terpenoids, and carotenoids are only a few types of marine natural products that have been discovered to possess strong antioxidant properties. This systematic review provides compelling evidence for the antioxidant potential of marine natural products. The research validates their potential as sources of novel antioxidants with various bioactive properties. Unlocking the full potential of marine natural products and integrating these discoveries into practical applications for enhancing human health and well-being calls for further research.

Keywords: 2,2-diphenyl-1picrylhydrazyl, marine algae, marine fungi, marine sponges, methanolic extract

INTRODUCTION

It has been established that the ocean, a complex ecosystem, is an excellent chemical and biological diversity source. Compared to non-marine microorganisms and terrestrial plants, marine organisms have been regarded as the most recent source of bioactive natural compounds, including 75% of all living organisms from 36 phyla (Balakrishnan *et al.* 2014). In recent years, marine natural products (MNPs) are the most promising source of bioactive compounds for drug discovery research (Nie *et al.* 2020). Bacteria, algae, sponges, and other marine organisms make many subgroups of substances.

These mentioned organisms are extremely promising sources of fascinating compounds that might be applied to food, cosmetics, pharmaceuticals, and other compounds essential to industry.

Despite the enormous potential of MNPs, the marine ecosystem still represents an extensive undeveloped reservoir of biologically active chemicals, which has considerable potential to contribute food components towards producing new functional foods (Mishra *et al.* 2023). In the world's seas, between 700,000 and one million different species can be found; however, only a small portion of all MNPs is being examined for their potential bioactivities (Mohamed *et al.* 2012, & Rotter *et al.* 2021). Due to the growing need by the food and pharmaceutical industries to produce natural bioactive anti-carcinogenic and anti-aging substances which provide significant health benefits, antioxidant activity has become intensively discussed and the focus of significant research (Balakrishnan *et al.* 2014). Seaweed and sponges are among the marine organisms with the highest levels of natural antioxidants (Muthiyan *et al.* 2018). Bioactive substances produced by the said organisms and the bacteria that live on them have been proven to be crucial for illness prevention and health promotion. The complex blend of phytochemicals exhibiting antibacterial, antioxidant, anticancer, and antiviral action is responsible for these positive effects. Sulfated polysaccharides, Phenolic compounds, sand organic acids are responsible for these activities (Balakrishnan *et al.* 2014).

Thus, to increase the availability and chemical variety of functional marine constituents, more research is needed to completely comprehend the biological activities of MNPs and their potential health advantages (Mohamed *et al.* 2012). The use of MNPs as a potential source of bioactivity has been discussed in a few recent review publications (Fonseca *et al.* 2023). However, only a few systematic literature reviews have focused on its potential as a source of antioxidants (El-Shafei, Hegazy, & Acharya 2021). Therefore, this review fills a gap in the existing literature by systematically reviewing the MNPs as a potential source of antioxidants.

METHODS

Study design and eligibility criteria

A review of literature conducted using a systematic search was employed using PRISMA guidelines. The following were used as inclusion criteria: (i) the study had to be focused only on primary research, such as experimental studies that looked into marine natural products as a source of antioxidants; (ii) it had to have used marine natural products, such as coral, seaweed, marine sponges, and other marine invertebrates, to look into anti-oxidant activity in humans; and (iii) the main outcome of interest was the antioxidant activity of marine natural products as measured by a recognized assay, e.g., ABTS, DPPH, FRAP, ORAC, etc., (iv) it had to be focused solely on antioxidant assays employing ethanolic and/or methanolic extracts, (v) the study had to be written in English, (vi) it had to be published between 2002 and 2022, and (v) had to be open-access, and peer-reviewed articles published in scientific journals. The study's inclusion criteria were all met by a total of 18 papers.

Search Strategy

The search engine Science Direct, Google Scholar, PubMed, and Mendeley, were used to obtain the most relevant articles by using the words "marine natural products," "marine natural resources," and/or "marine products" combined with "antioxidant," "antioxidants," and "antioxidant activity. Only English, open-access peer-reviewed articles with full text were considered, preferably published between 2002 and 2022.

Data Extraction

The search engine Science Direct, Google Scholar, PubMed, and Mendeley, were used to obtain the most relevant articles by using the words "marine natural products," "marine natural resources," and/or "marine products" combined with "antioxidant," "antioxidants," and "antioxidant activity. Only English, open-access peer-reviewed articles with full text were considered, preferably published between 2002 and 2022.

Study Selection

After removing duplicates from a total of 1244 independently downloaded papers, 1093 published articles remained. 37 articles' full-text versions were retrieved after their titles and abstracts were screened for further assessment. There are 19 articles with methods that still need to meet the inclusion criteria. In the end, only 18 qualified articles were used in this review, as illustrated in Figure 1.

RESULTS AND DISCUSSION

Studies of MNPs as Antioxidant according to Study Features

The analysis's results indicate the level of distribution of MNP studies as a potential source of antioxidants in terms of (a) publication year, (b) marine sources, and (c) marine species. Figure 2 below provides information on the frequency distribution of the studies based on the classified feature based on publication year.

Results revealed that out of the 18 qualified studies, only a few published studies focused mainly on the MNPs as a source of antioxidants

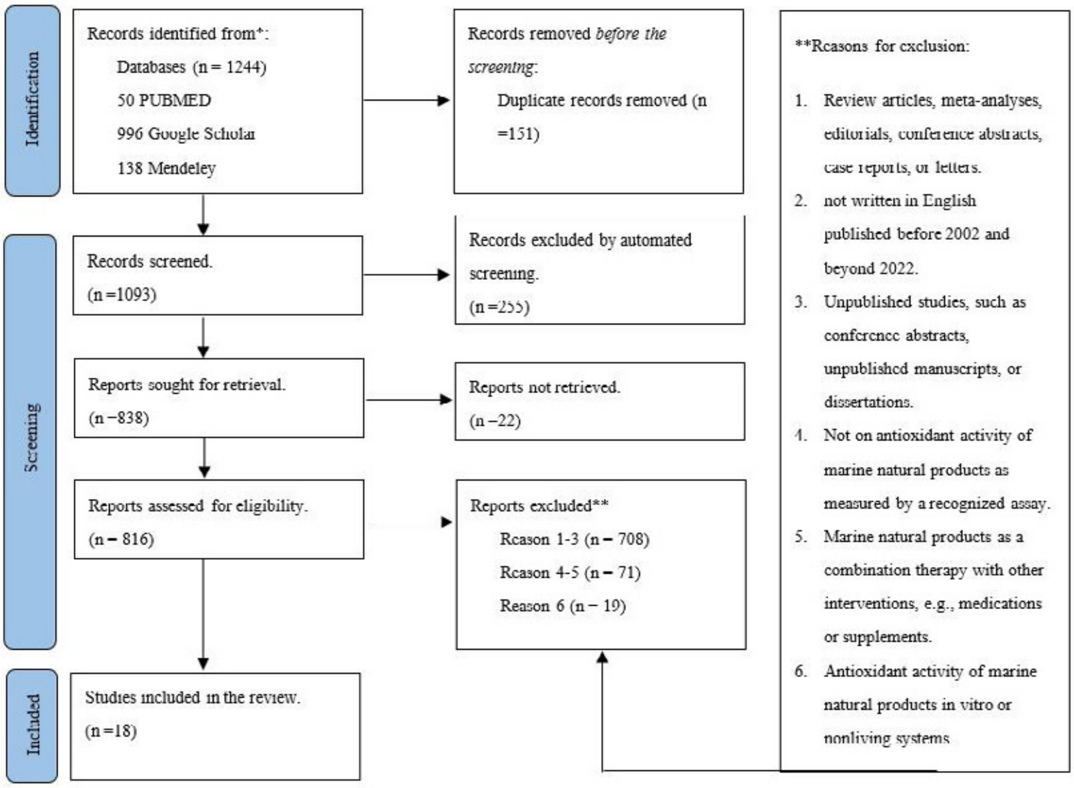

Figure 1 The flow of information for study selection (Adapted from McKenzie *et al.* 2021)

(2002-2012, 0; 2013, 2; 2014, 2; 2015, 3; 2016, 3; 2017,0; 2018,1; 2019, 1; 2020, 2; 2021, 3; 2022, 1). These indicate that the chemistry of marine sources, in general, has yet to be fully embraced by the field of MNPs, at the expense of its potential as antioxidants based on the inclusion criteria developed for the purpose.

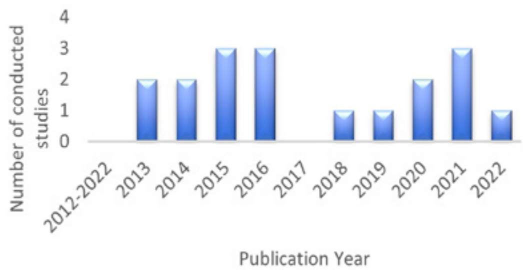

Figure 2 Frequency Distribution of Qualified Studies by Publication Year

The systematic review findings highlight the significant potential of marine natural products as a rich source of antioxidant compounds. As presented in Figure 4, although marine algae are the most studied and considered a rich source of natural antioxidants (Muthiyan et al. 2018), marine fungi have the highest number of species possessing high antioxidant potential.

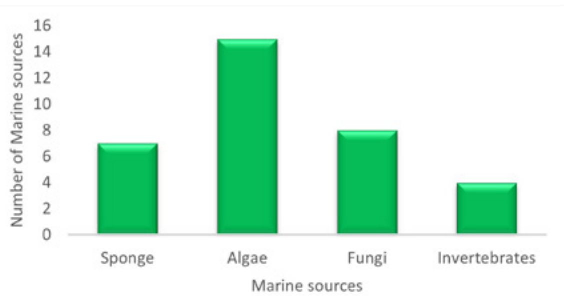

Figure 3 Frequency distribution of Marine Sources

Marine natural products as a source of antioxidant compounds

The data analysis showed that MNPs have much potential as a source of antioxidant compounds. Almost all the research included in the analysis mentioned MNPs' antioxidant activity. The abundance of antioxidants in various marine species, such as algae, fungi, sponges, and other invertebrates, is shown in Table 1.

Table 1 Marine natural product sources as potential antioxidants

Marine Source	Type	Species	Secondary Metabolites	Reference
Marine algae	Red algae	*Chlorococcum humicola*	Phenols Alkaloids Steroids	Kavitha & Palani (2016)
		Avrainvillea erecta	Flavonoids Phenols Tannins	Chai *et al.* (2015)
		Chondrophycus ceylanicus *Gelidiella acerosa* *Gracilaria corticata*	Alkaloids Saponins Flavonoids Tannins Glycosides	Lakmal *et al.* (2014)
		Chondrus crispus	Flavonoids Polyphenols	Alkhalaf (2021)
		Gracillaria edulis *Centerocerous clavulatum*	lipid soluble total chlorophylls	Leelavathi & Prasad (2014)
		Laurencia synderiae	Total phenolic Flavonoid	Karimzadeh & Zahmatkesh (2021)
	Green algae	*Chaetomorphacrassa* *Caulerpa racemosa*	Flavonoids *total carotenoids*	Lakmal *et al.* (2014)
		Spongomorpha indica	alkaloids Steroids Tannins Flavonoids	Rajasekaran (2022)
	Unspecified	*Cymodeace rotundata* *Gracillaria crassa* *Cymodeace serrulata*	*Not identified*	Leelavathi & Prasad (2014)
	Brown algae	*Sargassum cassifolium*	Alkaloids Saponins Flavonoids Tannins Glycosides	Lakmal *et al.* (2014)
Marine fungi	*Unspecified*	*Aspergillus versicolor*	aspermutarubrol/ violaceol-I	Yang *et al.* (2020)
	Pavona cactus	*Penicillium digitatum* *Hypocreaceae* *Sterigmocystis sp.*	butyrolactone I aspernolide E, phenolic derivative	Nie *et al.* (2020)
	Shark gill	*Aspergillus flavipes* *Penicillium polonicum* *Penicillium chrysogenum* *Penicilliium corylophilum*		

Marine Source	Type	Species	Secondary Metabolites	Reference
Marine Sponge	Unspecified	*Zyzzya fuliginosa*	alkaloids	Utkina (2013)
		Hyrtios erectus	Not identified	
		Aaptos suberitoides		
		Fascaplysinopsis reticulata		
		Xestospongia sp		
		Acanthella sp		
		Petrosia contignata		
Marine Invertebrates	Mollusks	*Littorina littorea*	Polyphenols	Borquaye *et al.* (2016)
		Galatea paradoxa		
	Sea cucumber	*Holothuria atra*	Flavonoid Terpenoid Phenols Saponin Glycoside	Murniasih *et al.* (2015)

Marine Algae

Marine macroalgae, also known as seaweed, is used as food in many countries. As a result, there is much interest in finding bioactive macroalgal metabolites to employ them as active components in developing functional foods, nutraceuticals, and pharmaceuticals (Mohapatra *et al.* 2013). In this context, searching for natural antioxidants in macroalgae is relevant to ongoing scientific interest and societal needs.

The fresh samples of *Chlorococcum humicola* in the study of Kavitha and Palani (Lakmal *et al.* 2014) were obtained from the Rameshwaram seashore in Tamil Nadu. The ethanol extracts showed considerable antioxidant capability in reducing power, DPPH, superoxide, and nitric oxide radical scavenging assays. Therefore, the algae *C. humicola* can be a substantial source of vital compounds that the pharmaceutical industry can utilize to produce medicines. Based on the GC-MS study's findings, 14 compounds were present, and their nature varied greatly. The analysis revealed that the 1-propene, 3-(2-cyclopentenyl)-2-methyl-1,1-diphenyl exhibited the most significant peak area (Figure 5). According to the analysis, flavonoids, alkaloids, and steroids are the metabolites responsible for antioxidant activity.

The marine macroalga *Avrainvillea erecta* (Berkeley) A. Gepp and E.S. Gepp (Family Dichotomosiphonaceae) that was discovered in the South China Sea off the southwest coast of Tinggi Island, Malaysia, was investigated by Chai *et al.* (2015). The findings showed that *A. erecta's* methanol extract and solvent fractions have the ferric reducing ability as well as scavenging 2,2-diphenyl-1picrylhydrazyl (DPPH), nitrogen oxide (NO), and hydrogen peroxide (H_2O_2). On the other hand, DPPH scavenging activity is correlated with the total phenolic contents. Therefore, the antioxidant activity of *A. erecta* extract revealed in the study is due to flavonoids and other phenolic components. The information showed flavonoids, phenols, and tannins are the main chemical components.

Fresh marine seaweeds were gathered from sample sites at the Beruwela coral reef in the Southern Province of Sri Lanka for the study by Lakmal *et al.* (2014). Among the methanolic extracts of the identified species such as red algae (i.e., *Chondrophycus ceylanicus, Gelidiella acerosa, Gracilariacorticata*), green algae (i.e., *Chaetomorphacrassa, Caulerpa racemosa*) and brown algae (i.e., *Sargassum cassifolium*); *C. racemosa* showed a significant average radical scavenging activity against DPPH (34.34%), alkyl (85.17%) and hydroxyl (81.16%), respectively. Green seaweed has the highest phenolic content and antioxidant activity of the three macroalgae categories (Mohamed *et al.* 2012). Alkaloids, saponins, flavonoids, tannins, and glycosides are some of the phytochemicals found in the species (Jayaseelan *et al.* 2014).

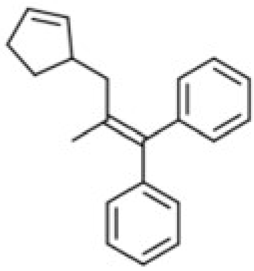

Figure 4 1-Propene, 3(2-cyclopentenyl)-2- methyl-1,1-diphenyl-

Red algae of the *Chondrus crispus* species from the Red Sea's coasts near Jeddah City were gathered for Alkhalaf's (2021) investigation. According to the findings, the methanolic extract made from the red algae species *C. crispus* had considerable antioxidant activity in the current investigation, and it successfully scavenged ABTS and DPPH free radicals in a dose-dependent manner. The extract's overall antioxidant capacity was also remarkable. The presence of flavonoids and polyphenols is thought to contribute to the antioxidant properties of several species of red algae, and the potency of this ability is correlated with the concentration of these bioactive chemicals (Zhang *et al.* 2019). Since flavonoids and phenols were also discovered in *C. crispus* extract, the antioxidant effects displayed by the extract in the current investigation could be attributed to these bioactive components.

Seaweed samples (Leelavathi & Prasad 2014) were collected from the Gulf of Mannar. *Cymodeace rotundata, Acanthopora spicifera, Ulva lactuca, Ulva reticulate, Turbinaria conoides, Gracillaria edulis, Kappaphycus alvarezii, Gracillaria crassa, Gracillaria foliifera,* and *Cymodeace serrulata* were the specimens identified. Petroleum ether and methanol were used to produce the extracts. By observing the decline in absorbance at 517 nm, the DPPH assays were performed to determine the antioxidant properties of seaweed. The highest overall antioxidant activity was demonstrated by *C. rotundata, G. crassa,* and *C. serrulata* in the methanol extract compared to other samples. Red algae samples were collected from the Chabahar coastlines at the coordinates (25° 18′ 53′′N; 60° 37′ 41′′E) in the Oman Sea, Iran, for the study of Karimzadeh and Zahmatkesh (2021). The red seaweed *Laurencia synderiae* was studied, and the results showed that different extracts (methanolic, chloroform, and ethyl acetate) have dose-dependent antioxidant activities. Future medication development is predicted to involve the significant identified compounds that have a strong biological impact on red algae, *L. snyderiae*. The most prevalent compounds are hexadecanoic acid (19.81%; Figure 6), oleic acid (8.34%; Figure 7), squalene (6.96%; Figure 8); and tetradecanoic acid (6.86%; Figure 9); as well as glycerin (8.62%;Figure 10), xylitol (8.46%; Figure 11), and squalene (8.96%; Figure 12). The red algae *L. snyderiae* has strong bioactive components that it can employ as a natural antioxidant and source of additional resources. Total phenolic and flavonoid concentrations are among its phytochemical components.

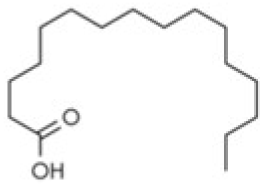

Figure 5 Hexadecanoic acid

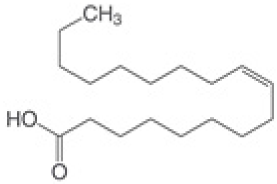

Figure 6 Oleic acid

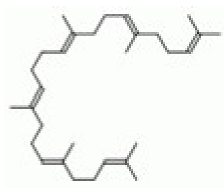

Figure 7 Tetradecanoic acid

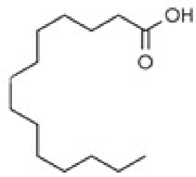

Figure 8 Glycerine

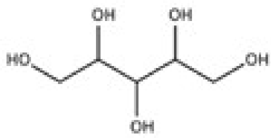

Figure 9 Xylitol

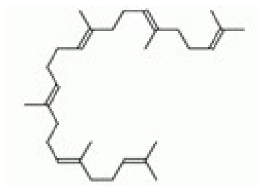

Figure 10 Squalene

The green macroalga *Spongomorpha indica* was gathered from the Visakhapatnam coastal area (Rajasekaran 2022). The phytochemical tests revealed the presence of potent active constituents such as alkaloids, tannins, steroids, and flavonoids, by which further GCMS analysis was conducted, and seven components were determined. The results of the physicochemical parameters tests were under WHO guidelines. Nonadecanoic acid (Figure 13) had the most significant peak area, around 47.006%, and the most prolonged retention period, 19.050.

Figure 11 Nonadecanoic acid

In the DPPH assay model, S. indica demonstrated a considerable dose-dependent reduction in the case of the DPPH radical. All the data demonstrated the highest levels of antioxidant activity, with superoxide scavenging activity displaying the most significant outcomes. Based on the findings, it was established that *S. indica* had powerful active ingredients with potent antioxidant activity.

Seaweeds were gathered from the station in Rameshwaram on the southern Indian coast of Olaikuda (N.Lat. 09°18.300' and E. Long. 079°20.096') for the study by Elangovan *et al.* (2019) The methanolic extracts of all the test species, including green algae *Enteromorpha intestinalis* and red algae *Gracillaria edulis*, exhibit high antioxidant activity (DPPH). The stated activity results from the high concentration of total chlorophylls that are lipid soluble, particularly Chl-a and related compounds, as well as the high concentration of total carotenoids.

Marine Fungi

In the study by Muthiyan *et al.* (2018), marine fungus strains were obtained from biological samples taken in the intertidal zone of Dalian, China (Utkina 2013), from shark gill tissues captured in the East China Sea, and from various corals in the Zhanjiang Sea region of China. The methanolic extracts of *Aspergillus flavipes, Hypocreaceae, Sterigmocystis* sp., *Penicillium digitatum, Penicillium polonicum, Penicillium chrysogenum,* and *Penicillium corylophilum* were some of the strain samples that showed DPPH free radical scavenging activity (scavenging ratios > 30% at 200 g/ml). Thus, found to exhibit antioxidant activity. The said antioxidants were assigned as Aspernolide E (Figure 14), butyrolactone I (Figure 15), a phenolic derivative, and possibly unidentified compounds.

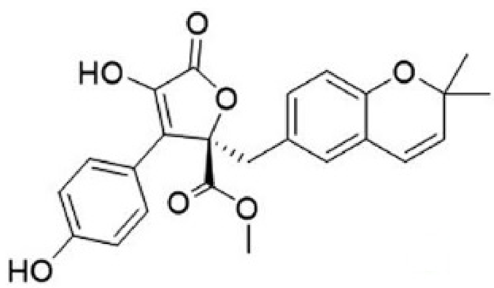

Figure 12 Aspernolide E

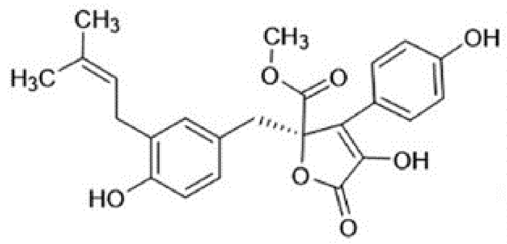

Figure 13 Butyrolactone I

The Aspergillus versicolor SH0105 fungus strain (Yang *et al.* 2020) was isolated from a deep-sea sediment sample from the Mariana Trench at a depth of 5455 m. The bioactive assay revealed that *A. versicolor* demonstrated a substantial reduction of Fe^{3+} and significant DPPH radical scavenging activity, which were more potent than ascorbic acid. This suggests discovering chemical entities with antioxidant activities from the marine medicinal microbial resources. Aspermutarubrol/violaceol-I (Figure 16) was identified as the chemical responsible for the antioxidant activity.

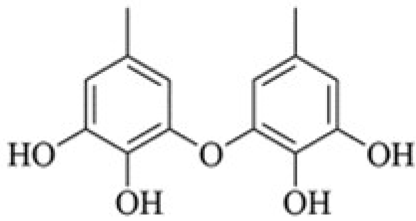

Figure 14 Aspermutarubrol/violaceol-I

Marine sponge

Many sedentary marine organisms, such as sponges, have acquired the capacity to create a variety of toxic substances to defend themselves against predators or to compete with other marine species (Paul *et al.* 2006). Sponges are receiving the most interest from the pharmaceutical industry because they produce the most bioactive secondary metabolites among all marine organisms. Alkaloids, steroids, terpenes, peptides, macrolides, and polyketides are only a few marine sponges' structurally diverse natural compounds (Dias *et al.* 2012).

The marine sponge *Zyzzya fuliginosa* (order Poecilosclerida) is a rich source of alkaloids with a pyrrolo[4,3,2-de]quinoline structure (Utkina 2013). The antioxidant properties of zyzzyanones A to D (1-4) and makaluvamines C, E, G, H, and L (Figure 17) were tested, which were isolated from the ethanolic extracts of the Australian marine sponge *Z. fuliginosa*. According to research on their effectiveness as radical scavengers, zyzzyanones and makaluvamines have moderate antioxidant activity, indicated by a phenolic function in the molecules.

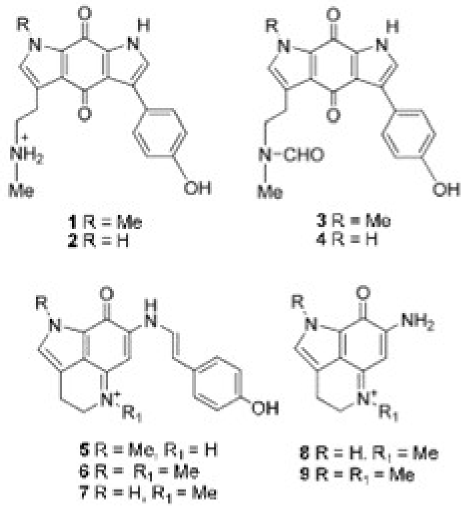

Figure 15 Structures of tested zyzzyanones and makaluvamines (Utkina 2013)

The marine sponge *Hyrtios erectus* was procured from the North Bay of the South Andaman Sea for the study of Muthiyan *et al.* (2018). According to the findings, the methanolic extract of *H. erectus* exhibited antioxidant activity against DPPH free radicals, superoxide anions, and hydroxyl radicals. With 50 µg/mL sponge extract, more than 50% inhibition (half inhibitory concentration) was observed. However, there is a need for further functional characterization of the bioactive compounds to determine the compound responsible for the activities.

Marine sponge species were gathered in Pecaron Situbondo, East Java, Indonesia, for the study of Abdillah *et al.* (2013). Results showed that only *Aaptos suberitoides* exhibited vigorous antioxidant activity in an assay using the DPPH method, as evidenced by an IC50 value of less than 30 mg/mL. In contrast, *Fascaplysinopsis reticulata, Acanthella* sp, *Petrosia contignata,* and *Xestospongia exigua* displayed moderate antioxidant activity, with an IC50 value of less than 100 mg/mL. The IC50 value for *Callyspongia* sp. and *Xestospongia* sp. was more significant than 100 mg/ml. The research has shown the high potential of *Xestospongia* sp, *F. reticulata, Callyspongia* sp, *Petrosia contignata,* and *Aaptos suberitoides* for developing bioactive chemical isolation as antioxidant agents.

Marine Invertebrates

Aquatic species' capacity for adaptation and survival in various habitats relies on their physical and chemical adaptations (Thakur *et al.* 2005). Bryozoans, mollusks, and other marine invertebrates all have soft bodies and sedentary lifestyles, making a chemical defense system necessary for survival. When introduced into their aqueous habitat, these compounds are rapidly diluted. The compounds must be very potent to be effective (Karimzadeh & Zahmatkesh 2021). Numerous researchers have investigated these environments in quest of biologically active molecules due to the high potency of chemicals used in aquatic defense systems and the requirement that they be water-soluble.

Molluscs

The two mollusks, *Littorina littorea*, and *Galatea paradoxa*, used in the study by Borquaye *et al.* (2016), were gathered from Labadi Beach in Accra and Sogakope on the Volta River. According to the IC50 values from the antioxidant experiments, methanol extracts are more effective at scavenging DPPH radicals than ethyl acetate extracts. Compared to the standard ascorbic acid medication, the methanolic extracts of *G. paradoxa* and *L. littorea* demonstrated outstanding DPPH radical scavenging ability, indicating they may be a good source of antioxidant chemicals. Polyphenols are one family of secondary metabolites with proven antioxidant action. Both *G. paradoxa* and *L. littorea* methanol extracts may have significant concentrations of these chemical compounds.

Sea cucumbers

Sea cucumber extracts from *Holothuria scabra, Holothuria atra, Holothuria leucospilota,* and *Holothuria excellens* were gathered from Jor Bay in East Lombok, Indonesia, for the study by Murniasih *et al.* (2015). Among the extracts, *H. leucospilota* and *H. atra* have strong antioxidant properties, particularly for DPPH method-based radical scavenging activity. The phytochemicals flavonoid, terpenoid, phenols, saponins, and glycoside were the constituents of *H. leucospilota* and *H. atra*. According to the results of the GC-MS study, 3-chloro-4-hydroxybenzoic acid (Figure 18) was found to be one of *H. atra's* active antioxidant components. This phenolic substance is crucial for its antioxidant effects.

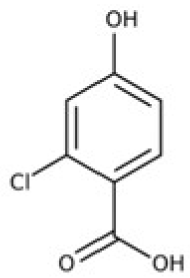

Figure 16 3-chloro-4-hydroxybenzoic acid

A wide variety of marine natural compounds with antioxidant activity were shown in the identified investigations. The polyphenols group, which includes flavonoids, alkaloids, phenols, and tannins, was the most frequently mentioned class of chemicals with antioxidant activity. Saponins, glycosides, terpenoids, and carotenoids are a few more types of chemicals that have been found to possess antioxidant activity.

CONCLUSIONS

According to the systematic review's findings, there is growing evidence that many bio-logically active chemicals with antioxidant properties can be found in the marine environment (Mehbub, Franco & Zhang 2014). Flavonoids, alkaloids, phenols, tannins, steroids, saponins, glycosides, terpenoids, and carotenoids, are just a few of the structurally diverse natural compounds that MNPs are a highly rich source. According to several screening studies, marine-derived methanolic and ethanolic extracts exhibit potent antioxidant activity.

This review provides compelling evidence for the antioxidant potential of marine natural products. The research validates their potential as sources of novel antioxidants with a range of bioactive properties identified from MNPs and positions them as potential therapeutic options in the future. Thus, it is recommended that the identification and functional characterization of the bioactive molecules necessary for the activities are needed. Unlocking the full potential of marine natural products and integrating these discoveries into practical applications for enhancing human health and well-being calls for further research.

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