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REVIEW

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The marine sponge genus *Dysidea* sp: the biological and chemical aspects—a review

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Abstract

Background Marine sponges and other marine invertebrates are considered hidden treasures for a variety of secondary metabolites with pharmacognostic and pharmacological activities which have the potential to create future "super drugs."

The main body of the abstract *Dysidea* species is one of the most widely distributed sponge species in the world which is found mainly near the shores of the Red Sea, Australia, Yap State, and the Philippines. *Dysidea* species are considered a source of bioactive natural metabolites that exhibit outstanding chemical diversity. They revealed polybrominated diphenyl ethers, sesquiterpene hydroquinones, furano-sesquiterpenes, diterpenes, chlorinated diketopiperazines, and Amino acids. They showed a broad spectrum of potent biological activities, such as antimicrobial, antimalarial, anti-inflammatory, antitumor, potent cytostatic, antifungal, and antioxidant activities.

Conclusion This review presents an overview of the isolated secondary metabolites from *Dysidea* species, and their recorded biological activities covering the published reports in the last 30 years.

Keywords Marine sponges, *Dysidea*, Active metabolites, Antimicrobial, Anti-inflammatory, Cytotoxicity

Background

The marine ecosystem is thought to be a source of bioactive substances and potential pharmaceuticals. Oceans represent 70% of the earth's area. About 33–34% of animal phyla live in the marine environment [1]. There are over 1000 distinct species per square meter in tropical regions, demonstrating the remarkable biological variety. A wide range of secondary metabolites have been produced as a result of environmental pressures such as competition for nourishment, space, and defenses. [2]. Marine sponges have been considered a hidden treasure for the past 50 years, due to the variations in their secondary metabolites [3, 4]. With the discovery of sponge-derived compounds, more than 14,000 different products have been recorded, many of which are currently undergoing clinical trials, for the treatment of cancer, pain, or other diseases [5]. Over 30% of the 18,000 marine products established come from sponges, and of the latest patent registrations for natural anticancer agents, more than 75% come from sponges. [6]. Sponges lack true tissue but instead have different cell types with different functions that work together to carry out normal body functions. A large amount of seawater is filtered to provide food and oxygen to the sponges, as well as to excrete waste products. Many sponges have a symbiotic relationship with microorganisms. Archaea, cyanobacteria, bacteria, fungi, and microalgae are examples of symbionts [6]. The history of sponges and medicines can originate back to Alexandrian physicians and was described in detail by the Roman historian Plinius [3]. Among various types of sponges, those belonging to the genus *Dysidea* were investigated for their active metabolites resulting in the isolation of several chemically and biologically unique and important molecules [7]. Many

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studies were done on the collection, chemical study, and the distinguishing of some species of the genus *Dysidea* (family Dysideidae) [8]. Sesquiterpenes, diterpenes, new sterols, and a structurally intriguing and extraordinarily diversified variety of metabolites have all been shown to be present in this sponge genus [9]. To our knowledge, no reviews on *Dysidea* were done since 2009. Our study aimed to collect the previously published studies, to discuss the achievements made over the past 30 years to address the prospective applications of biomolecules identified from *Dysidea* sponge, and to consider the possible future research directions in this field.

Methods

Databases including Wiley Online Library (WOL), Pub Med, and Google Scholar were accessed electronically. Upon typing (*Dysidea*), there were 232 hits, 2 books, and 13,200 on PubMed, WOL, and google scholar, respectively. Type in "*Dysidea*," "Sesterterpenes," "*Dysidea* pharmacological activities," or "*Dysidea* species" were eligible materials for writing this review. The investigations of *Dysidea* species, active metabolites, antimicrobial evaluation, and therapeutic potential were taken from published peer-reviewed scholarly journal articles, online resources, conference papers from conference proceedings, and book chapters (Fig. 1).

Main text

Geography and taxonomy of Dysidea

Sponges' taxonomy usually relies on the composition of their skeletal materials [10] and their morphological properties. They can have spicules made of calcium, silica, or protein-based sponging fibers (Class Hexactinellida, Class Calcarea, and Class Demospongiae). As shown in Fig. 2, *Dysidea*-related sponges are members of the Class Demospongiae, Order Dictyoceratida, and Family Dysideidae. The basic skeleton of these sponges is made up of reticulation of sponging fibers and lacks mineral spicules. According to Munro and Blunt, the genus *Dysidea* has 17 identified species so far [10–13].

As seen in Fig. 3, the genus *Dysidea* was reported in many areas of the world from tropical regions to America and from the Red Sea to the Indo-Pacific regions [10, 14] but it is mainly found in subtropical and tropical regions [9].

Phytochemical profile of Dysidea sp.

As shown in Fig. 4, the *Dysidea* sp. contains various classes of active metabolites with sesquiterpenes being the most distributed chemical class.

Polybrominated phenyl ether

The early studies on the sponge *D. herbacea* illustrated the identification and isolation of five polybrominated 2-phenoxyphenol **(1–5)** derivatives from the Western Caroline Islands (presumably Palau). These compounds were proven to show antimicrobial potential against Gram-positive and Gram-negative bacteria. *D. chlorea* contained only 2-(2,4-dibromophenoxy)-4,6-dibromophenoxy) **(6)** [15]. The sponge *D. fragilis* afforded a new hexabromodiphenyl ether (7) and a brominated diphenyl ether. Polybrominated oxydiphenol **(8–12)** derivatives were identified from random collections of *D. herbacea* from Fijian and the Great Barrier Reef. Compounds such as diphenyl ethers **(13)** were previously isolated from *D. herbacea*, with differences in the oxygen on both phenyl rings found in them instead of only one [16].

The chlorinated metabolites from *Dysidea* show the strongest resemblance to the metabolite of blue-green algae. The marine sponge *D. herbacea* from tropical areas exhibited large numbers of unique polychlorinated compounds found in the whole sponge tissues [16, 17] where a new series of polychlorinated amino acid derivatives were isolated from this particular sponge. Two hexa-chlorinated metabolites, dysideathiazole **(14)**, and N-methyldysideathiazole **(15)** were found as majors in addition to a minor pentachlorinated compound, and 10-dechloro-N-methyldysideathiazole **(16)** was isolated from a specimen from Pohnpei [16]. Arenastatin A **(17)** from *D. arenaria* is a cyclic depsipeptide isolated from an Okinawan marine sponge and exhibited extremely potent cytotoxicity against KB cells at IC_{50} 5mg/ml [18].

Azabicyclo propene derivatives

A novel and unique azacyclopropene carboxylic acid ester, dysidazirine (18) has been identified from *D. fragilis,* and the structure was elucidated using spectral data in addition to four new azacyclopropene derivatives were separated by Faulkner et al. [19], from the same species collected from Pohnpei. The Pacific Island *D. herbacea* investigation resulted in the isolation of dysideathiazoles which are considered new polychlorinated amino acid derivatives [16]. A minor constituent of a Papua New Guinea specimen of *D. herbacea* [20] revealed Herbamide A **(19)** which is a chlorinated amide, while the sponge *D. fragilis* collected from south China demonstrated a new diketopiperazine named Dysamide D **(20)** [21] as seen in Fig. 1.

Sesquiterpenes

Sesquiterpenes can be established as genuine taxonomic markers for this specific genus. A Barrier Reef collection of *D. herbacea* followed by extensive studies of the

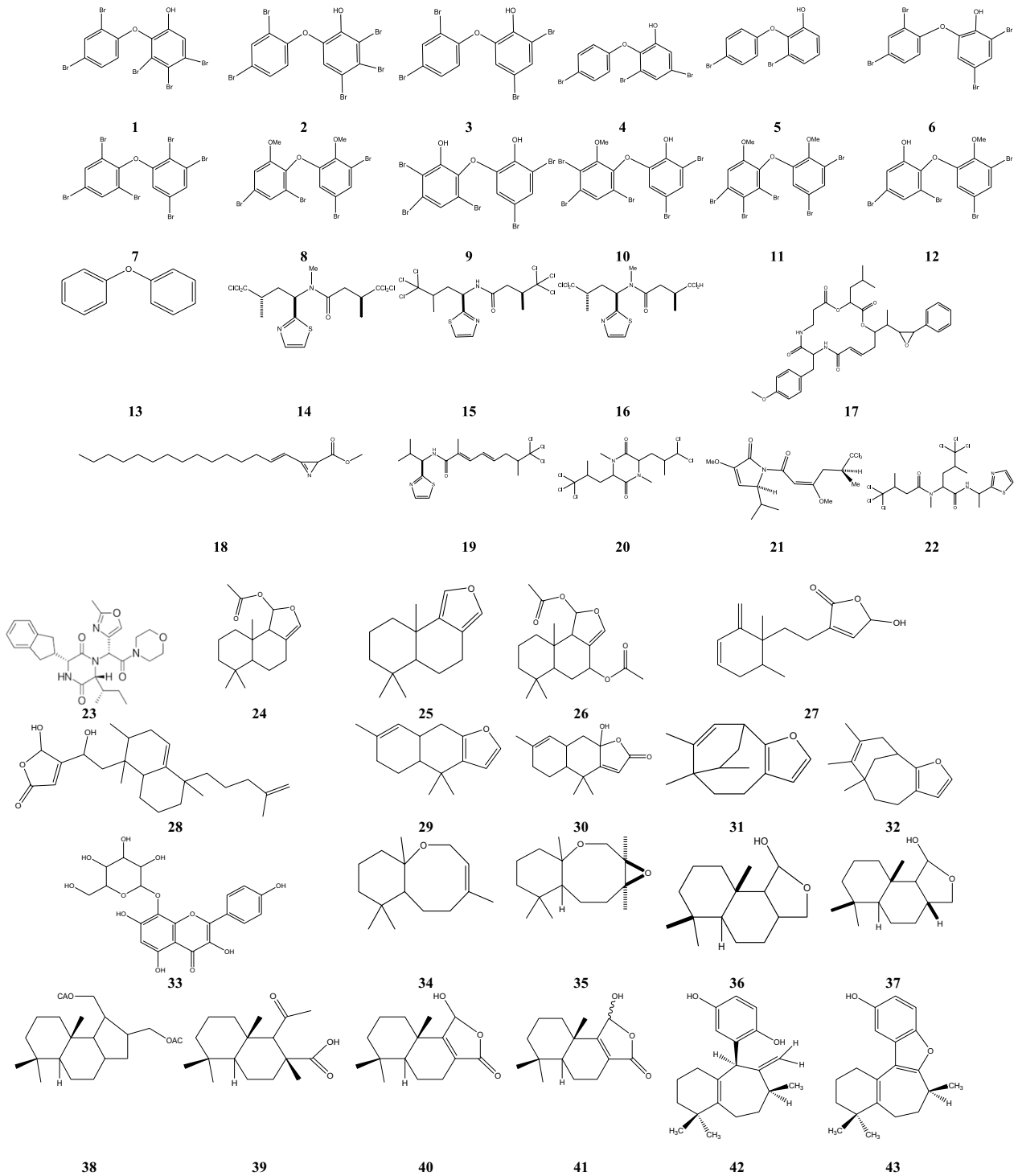
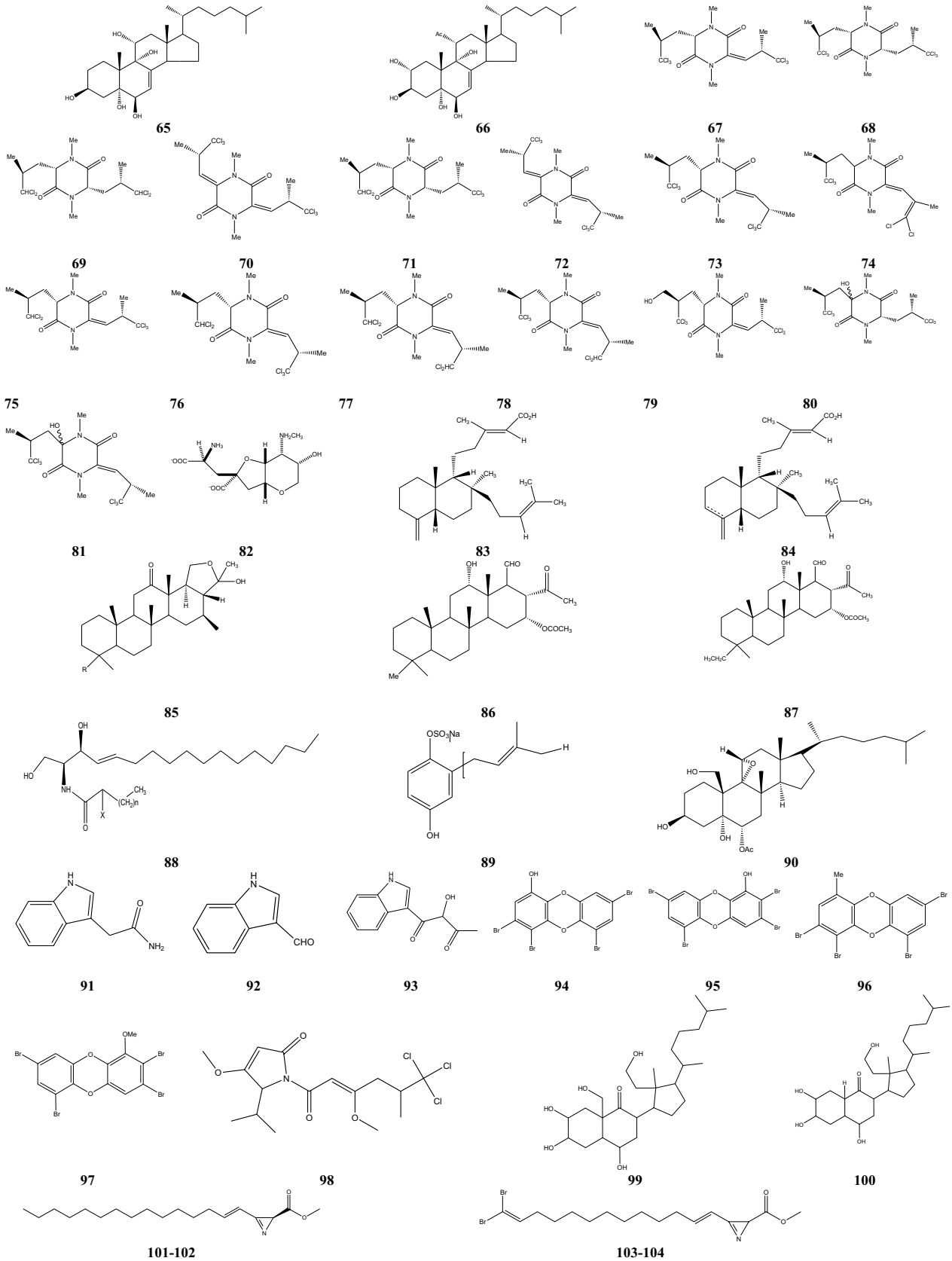


Fig. 1 Active metabolites isolated from different *Dysidea* sp



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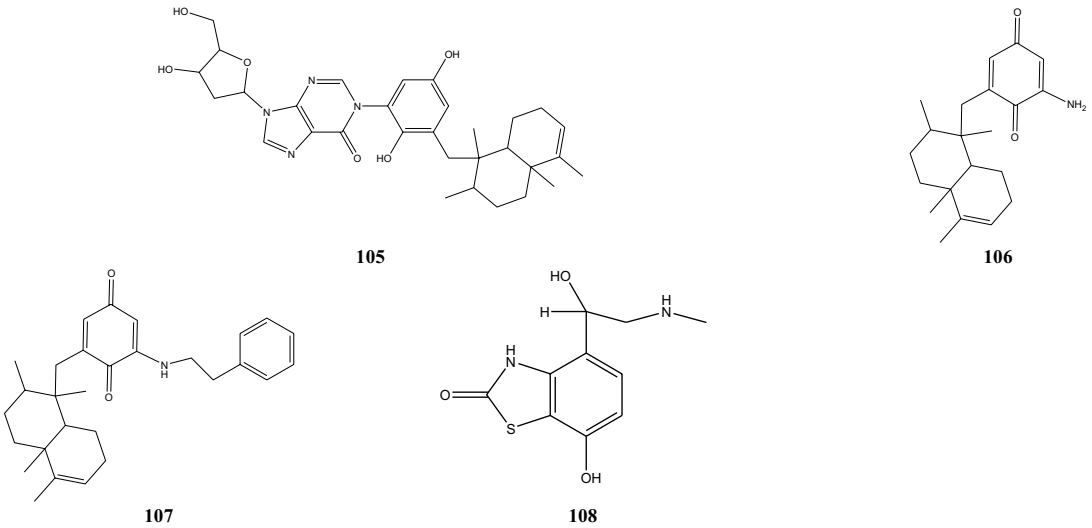

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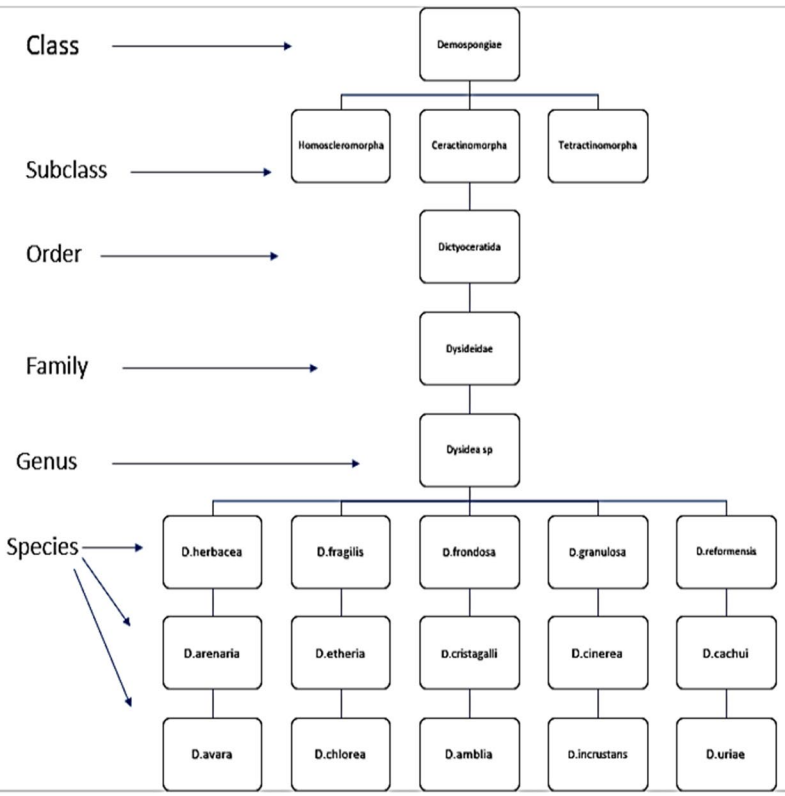

Fig. 2 *Dysidea*-related sponges are members of the Class *Demospongiae*, Order *Dictyoceratida*, and Family *Dysideidae*. The basic skeleton of these sponges is made up of reticulation of sponging fibers and lacks mineral spicules. There are more than 15 species discovered so far including *D. avara*, D. Herbaceae, *D. fragilis*, *D. chlorea*, *D. amblia*, *D. arenaria,* and *D. etheria*

isolated compounds using X-ray revealed many sesquiterpenes such as dysinin **(21)**, dysidenin **(22)** [22, 23], and diketopiperazine **(23)**. Drimane sesquiterpene, 7-deacetoxy-olepupuane **(24)**, related to the marine compound euryfuran **(25)**, and olepupuane **(26)** from *D. herbacea* were also recorded [24]. *D. herbacea* chloroform

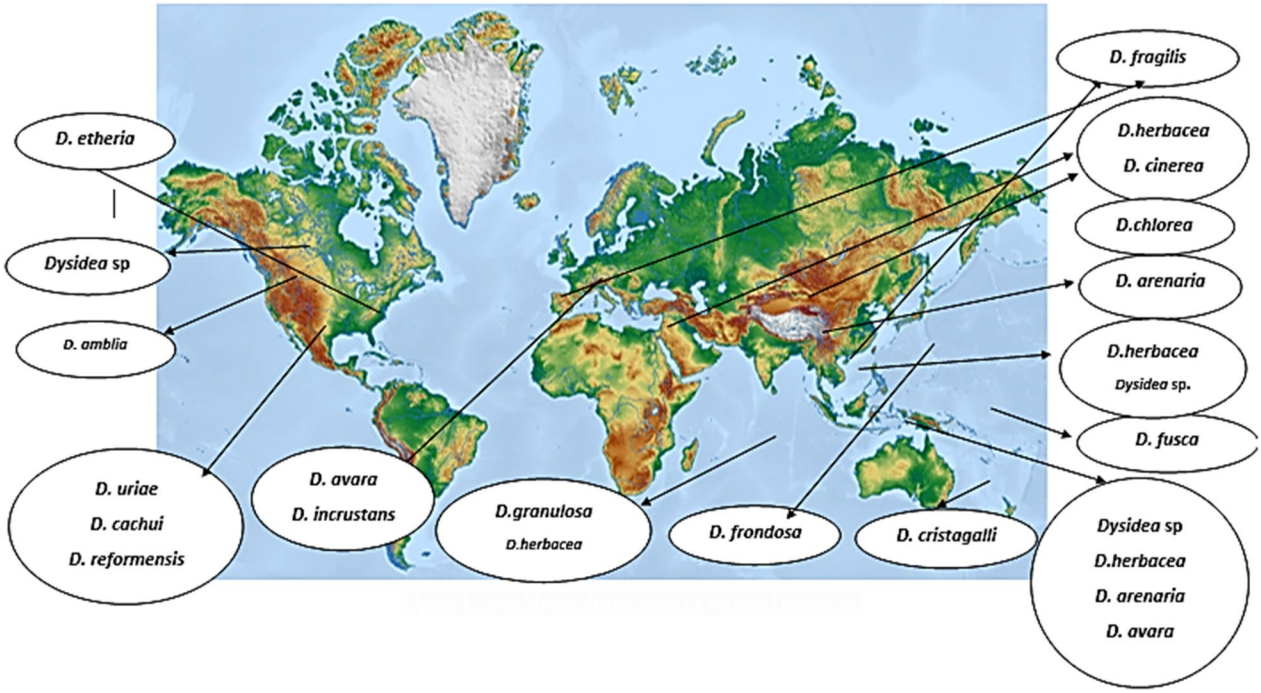

Fig. 3 Geographical distribution of genus *Dysidea*. Many areas of the world from tropical regions to America and from the red sea to the Indo-Pacific regions but it is mainly found in tropical and subtropical regions. *D. herbacea* is found in the Pacific Ocean and the Red Sea, *D. avara* is mainly located in South America and Peru, and the great barrier reef is the habitat for many species such as *D. herbacea, D. arenaria,* and *D. avara*

extract afforded the furano-sesquiterpene, herbacin and a new sesquiterpene hydroxybutenolide **(27)**, and one of them was obtained as oil which is Dysidiolide **(28)**. A collection of *D. etheria* from Bermuda contained furodysinin **(29)** and furodysinin lactone **(30)** [25]. Nakafuran-8 **(31)** and nakafuran-9 **(32)** are two furano-sesquiterpenes from the Hawaiian sponge *D. fragilis* in addition to a novel sesquiterpene aldehyde and penlan furan. An unusual β, γ-Epoxy γ-Lactone, and dysether has been isolated from *D. etheria*. Herbacin **(33)** is a furan sesquiterpene that is a major metabolite of *D. herbacea* collected in India [26]. In the marine environment, some compounds such as drimanes can be found in marine as well as terrestrial organisms [27, 28]; they have been found in many sponges of the genus *Dysidea*. Arenaran-A **(34)** and arenaran-B **(35)** were reported from the sponge *D. arenaria* [14], drimane **(36)**, five new drimane sesquiterpenes isomers **(37–41)** from *D. fusca* [29], sesquiterpene-hydroquinones from both *D. cachui* and *D. reformensis*, and a furano-sesquiterpene dendrolasin from *D. uriae*, respectively [30]. It was noted that the ethyl acetate fraction of *D. frondosa* obtained from Pohnpei yielded six sesquiterpenes and frondosins **(42–47)** all of them possessed new carbon skeletons and were proven as low micromolar range inhibitors of protein kinase C and interleukin-8 receptors [31]. Avarol **(48)** obtained from *D. avara* is a potent cytostatic, antitumor agent, and antibacterial sesquiterpenoid hydroquinone. Avarol makes up roughly 6% of the dry weight of the sponge, making it the most prevalent chemical in the crude extract. Another series of sesquiterpenes have been characterized from *D. herbacea*. They are furodysin, thiolfurodysin **(49)**, and thiolfurodysinin **(50)** (previously reported from an unidentified *Dysidea* species [25].

Diterpenes

Diterpenes are a class of marine natural substances with a wide range of biological functions. *D. amblia* located at Pt. Loma, San Diego, CA was extensively studied and yielded Ambliol C **(51)**, ambliofuran **(52)**, pallescensin A **(53)**, pallescensolide **(54)**, and ambliol B **(55)**. The structures of those compounds were elucidated using spectral data such as H NMR; then, they were reassigned by X-ray diffraction which was proven to have a trans-fused decalin ring system rather than the cis ring junction. Furan-diterpene ambliol-A **(56)** is established as a major metabolite of marine sponge *D. amblia* [32].

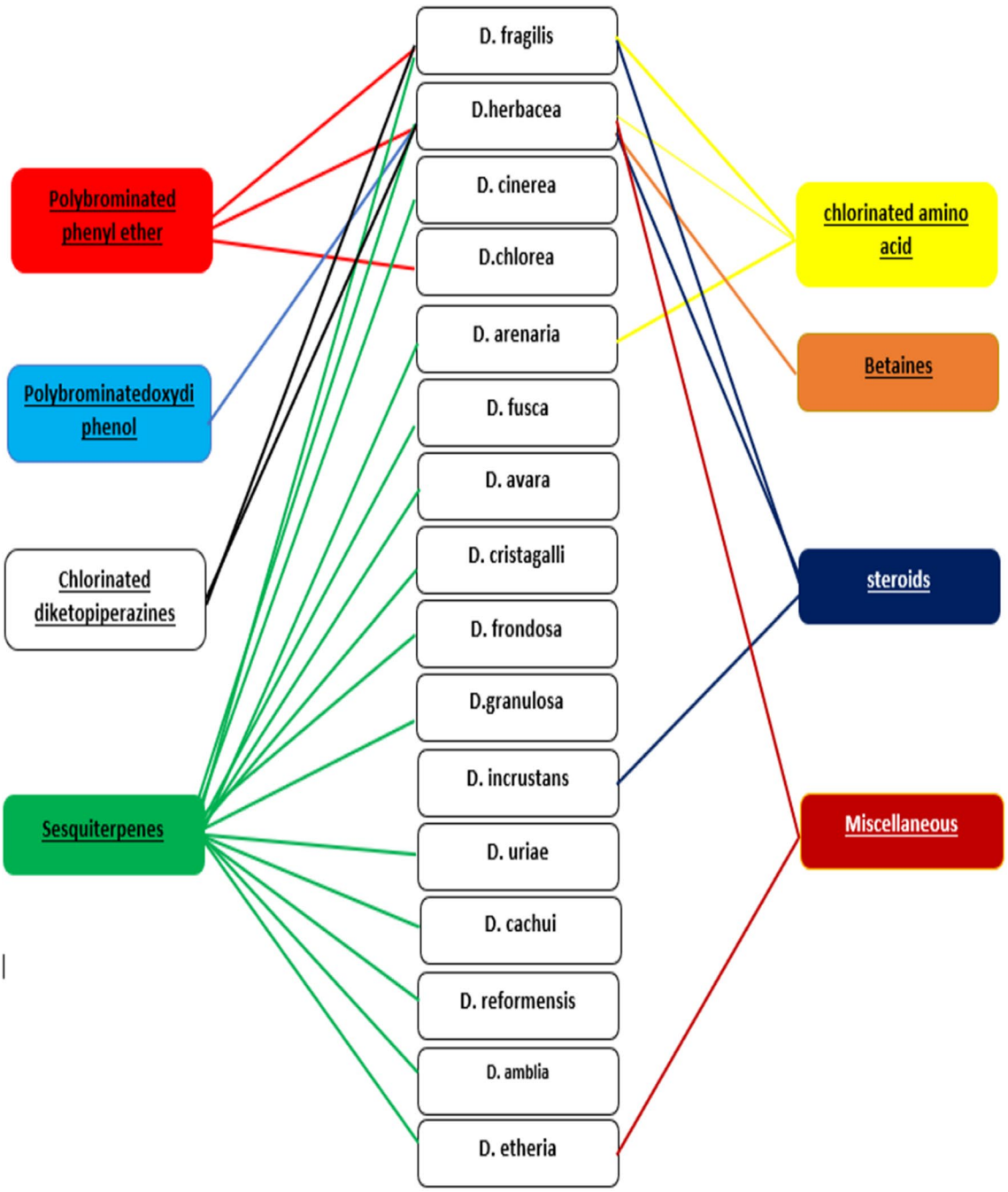

Fig. 4 Major classes of active metabolites identified from various species of *Dysidea* sp. They included a variety of compounds including sesquiterpenes, steroids, phenyl bromo ethers, amino acids, DKPs, poly brominated oxyphenols, diterpenes, and betaines

Betaines

D. herbacea from Yap state gave new betaines, dysibetaine PP **(57)**, dysibetaine CPa **(58)**, and dysibetaine CPb **(59)**. Dysibetaine PP was proven as a novel dipeptide betaine [33], while **(58)** and **(59)** were assessed as unprecedented cyclopropane betaines. Nevertheless, compounds **(58)** and **(59)** demonstrated weak affinity toward the kainic acid-type glutamate and N-methyl-D-aspartic receptors, respectively, in a radioligand binding assay [34, 35].

Chlorinated diketopiperazines

The terpene and the di-N-methyl substituted diketopiperazine, as well as their dichloro analog, were the two main metabolites found in *D. herbacea* from One Tree Island. The Ficoll (cellular extract) and Percoll (tissues extract) fractions were analyzed by NMR (for diketopiperazines), and also Dysidamide D (20) from *D. fragilis* [19, 36–38]. Chlorinated diketopiperazines such as dihydrodysamide C **(60)** and didechlorodihydrodysamide C **(61)** along with spirodysin **(62)** are the major metabolites found in *D. fragilis*, and their presence may be attributed to the bacteria or fungi that inhabit it [39].

Steroids

The investigation of *D. incrustans* found near the coasts of Tunisia from the Mediterranean Sea resulted in polyoxygenated steroids: incrustasterol A **(63)** and B **(64)**. Their unique structures included a rare σ, 11-keto with other oxygenated functions on the rings A and B that were confirmed by spectral data interpretation [40].

Ketones

Numerous biologically active substances contain hydroxy ketones (ketols). The dihydroxyketone side chain is an important structural element of adriamycin, a strong anticancer agent, in addition to being shared by a wide range of anti-inflammatory medications (corticosteroids). Furthermore, because polyoxygenated steroids have been identified from marine organisms and are thought to be a developing collection of metabolites with potential biological and pharmacological activity, such functionalization of steroid substrates is significant [41].

Sterols

As seen in Fig. 1, *D. fragilis* revealed two new polyhydroxylated sterols [42]. They are biosynthesized from cholesterol [43]. *D. chlorea* obtained from the Federated States of Micronesia gave more than nine new polychlorinated diketopiperazines **(73–81)**, along with six previous ones **(67–72)** [36]. Dysamide A **(68)** and N-demethyl2,3-dihydrodysamide C along with significant known sterol (24 Z)-24-ethyl-cholesta-7(8),24(28)-diene-3β,5α,6β-triol) were isolated before from *D. herbacea and D. fragilis* as well.

D. arenaria and *D. etheria* have been noted to produce sterols [44], aglycones, and other hydrocarbons without the aromatic moiety. The characterization of eight new polyhydroxylated sterols was established and shown to possess cytotoxic activity.

Amino acids

Dysiherbaine (82) is an amino acid with high epileptogenic potential, obtained from the marine sponge *D. herbacea* [45]. It was proven to induce characteristic epilepsy-like symptoms in mice and has been confirmed as the most potent epileptogenic excitatory amino acid yet identified [46].

Sesterterpenes

They are frequently found in marine species' secondary metabolites and plants. Their range in structural complexity includes carbo tricyclic ophiobolanes, polycyclic anthracenones, polycyclic furan-2-ones, and polycyclic hydroquinone, in addition to other carbon skeletons. Bilosespens A **(83)** and B **(84)** were obtained from the Red Sea sponge *D. cinerea* [47] from Dahlak archipelago, Eritrea. Spectroscopic investigation, namely 1D and 2D NMR data, was used to determine the structure of the mixture of the two irreconcilable compounds. The mixture of bilosespens A **(83)** and B **(84)** can act as an anticancer agent against human cancer cells. [48].

Miscellaneous

In addition to the above-classified compounds from the genus *Dysidea,* the following compounds have been isolated. On the one hand, six new biologically interesting alkylated saclarins, scalardysin A & B **(85)**, scalarherbacin A **(86)**, scalarherbacin B **(87)**, and acetates of scalarherbacin A & B have been isolated from *D. herbacea*. On the other hand, *D. etheria, and D. arenaria* yielded ceramide **(88)**, new hexa-prenyl hydroquinone sulfate **(89)** and sterol 9R,11R-epoxycholest-7-ene-3â,5R,6R,19-tetrol 6-acetate (ECTA) **(90),** respectively. Their biological activity varied from inhibition of proton potassium ATPase [10] to the reversal of fluconazole resistance mediated by a *Candida albicans* MDR efflux pump [44].

Indoles are among other classes isolated from *D. etheria.* Indole-3-acetamide **(91)**, indole-3-carboxaldehyde **(92)**, and 4-hydroxy-S-(indole-3-yl)-S-oxo-pentan-2-one **(93)** were reported. This is the first time for the isolation of indoles from this genus of sponge and a sponge-derived plant growth regulator. In the lettuce seedling assay, the recognized auxin indole-3-acetamide is also effective at promoting root growth [49].

Australian *Dysidea sp* revealed new cytotoxic tetrabromo-dibenzo-p-dioxins derivatives namely spongiadioxins A **(94)** and B **(95)**, along with their methyl ethers **(96, 97)**, respectively. Elucidation of those compounds was established by 2D NMR spectroscopy, in addition to X-ray analysis [50]. The marine sponge *D.*

Table 1 Pharmacological activities of active metabolites derived from various *Dysidea* sp

Compound number	Pharmacological activity	Species name	Compound name	References
1–6	Broad-spectrum antimicrobial activity against Gram-positive and gram negative bacteria	*D. herbacea* and *D. chlorea*	Polybrominated 2-phenoxyphenol and 2-(2,4-dibromophenoxy)-4,6-dibromophenoxy)	[54, 55]
7	Antimicroalgal against various classes of algae	*D. fragilis*	Hexabromodiphenyl ether and brominated diphenyl ether	[15]
8–16	Antifungal activity, broad-spectrum antimicrobial	*D. herbacea*	Polybrominated oxydiphenol, diphenyl ethers, dysideathiazole N-methyldysideathiazole, and 10-dechloro -N-methyldysideathiazole	[56, 57]
17	Extremely potent cytotoxicity against KB cells	*D. arenaria*	Arenastatin A	[18]
18	Cytotoxic against L1210 cells. Inhibition the growth of bacteria such as *Pseudomonas aeruginosa*,, and fungi such as *Candida albicans*	*D. fragilis*	Dysidazirine	[51]
19	Antileishmanial activity	*D. herbacea*	Herbamide A	[38]
20	Toxic compound	*D. fragilis*	Dysamide D	[21]
21, 22	Antimicrobial, and inhibits the growth/development of *H. contortus* larvae	*D. herbacea* and *D. fragilis*	Dysinin Dysidenin	[58]
23	Anti-inflammatory, Antibacterial, cardiovascular diseases, and antiviral		Diketopiperazines	[59, 60]
24	Antimicrobial with antifungal activity		7-deacetoxy-olepupuane	[61]
(25–27)	Antiviral, cytotoxic and leishmanicidal activities		Euryfuran, Olepupuane, and Hydroxybutenolide	[62, 63]
(28–30)	Cancer and other proliferative diseases may be treated with the use of their antimitotic activity	*D. etheria*	Dysidiolide, Furodysinin, and furodysinin lactone	[64]
31, 32	Cytotoxic activity	*D. fragilis*	Nakafuran-8 O-methyl nakafuran-8 lactone nakafuran-9	[65]
33	Inhibit rat brain nitric oxide synthase activity	*D. herbacea*	Herbacin	[66]
34, 35	Anticancer potential against several types of cancer cells	*D. arenaria*	Arenaran-A and arenaran-B	[14, 66]
(36–41)	Toxic compounds	*D. fusca*	Drimane and drimane sesquiterpenes	[29, 67]
(42–47)	Inhibition of interleukin-8 receptors and anti-inflammatory	*D. frondosa* and *D. crista galli*	Frondosins and sesquiterpenes	[31, 68]
(48–50)	Antiparasitic, and anthelmintic	*D. herbacea,* and *D. fragilis*	Furodysin, thiolfurodysin, and thiolfurodysinin	[69, 70]
(51–56)	Antitumor and antimicrobial	*D. amblia*	Ambliol c, Ambliofuran, Pallescensin a, Pallescensolide, and Ambliol b,	[30, 71]
(57–59)	Glutamate receptor agonist, potent epileptogenic excitatory amino acid, and α-glucosidase inhibitors	*D. herbacea,*	Dysibetaine pp, Dysibetaine cpa, and Dysibetaine cpb	[34, 72, 73]
(60–62)	Cytotoxic, and inhibit protein phosphatase	*D. herbacea* and *D. fragilis*	Dihydrodysamide c, Didechlorodihydrodysamide c, and Spirodysin	[74–77]
(63, 64)	Cytotoxic	*D. incrustans*	Polyoxygenated steroids. (Incrustasterol a and b)	[78, 79]

Table 1 (continued)

Compound number	Pharmacological activity	Species name	Compound name	References
(65, 66)	Highly oxygenated sterols with cytotoxic activity	*D. etheria, D. aff. frondosa*, and *D. fragilis*	Polyhydroxylated sterols	[42, 51, 80]
(67–72) (73–81)	Prevention of fertilized sea urchin eggs from further division	*D. chlorea*	Heterumadysins	[10]
(82)	Neurotoxic, and potent epileptogenic amino acid	*D. herbacea*	Dysiherbaine	[81, 82]
(83,84)	Cytotoxic against several cancer cells	*D. cinerea and D. avara*	Bilosespens(a,b), avarol	[48]
(85,86)	Cytotoxic Scalarane sesterterpenoids	*D. etheria* and *D. herbacea*	Scalardysins	[83]
(87)	Antitumor and antimicrobial	*D. amblia*	Diterpenes	[30, 32]
(88)	Antimicrobial, cytotoxic and anticonvulsant activity	*D. robusta*	Ceramide	[84]
(89)	Antiproliferative potential against various cancer cell lines	*D. granulosa*	Granuloses A	[85]
(90)	The first marine natural substance to treat resistant strains of *C. albicans*	*Dysidea arenaria*	9α,11α-Epoxycholest-7-ene-3β,5α,6α,19-tetrol 6-Acetate (ECTA)	[44]
(91–93)	Promotes root growth regarding the lettuce seedling assay and act as antifungal	*Dysidea* sp.	Indole-3-acetamide Indole-3-carboxaldehyde 4-hydroxy-s-(indole-3-yl)-s-oxo-pentan-2-0ne	[86–88]
(94–98)	Cytotoxic and inhibit the bacterial α-D-galactosidase and antimicrobial	*D. dendyi and D. herbacea*	Tetrabromodibenzo-p-dioxins, spongiadioxins a and b, and Dysidin	[50, 89] [38]
(99, 100)	Antiviral, ichthyotoxic, antimicrobial, anti-inflammatory, antiproliferative, and anti-fouling	*D. herbacea* and *D. fragilis*	Herbasterol and 19-norherbasterol	[90, 91]
(101–104)	Cytotoxic against l1210 cells and inhibited the growth of *Candida albicans*	*D. fragilis*	(4e)-s-dysidazirine (4z)dysidazirine (4e)-antazirine (4z)-antazirine	[51, 92, 93]
(105–107)	Anti-invasion potential	*Dysidea* sp.	Avinosol 3′-aminoavarone 3′-phenethylaminoavarone	[52, 94]
(108)	A novel β_2-adrenoceptor selective agonist	*Dysidea* sp.	β_2-adrenoceptor agonist S1319	[53]

herbacea demonstrated dysidin **(98)** and a new ichthyotoxic 9, ll-secosterol, and herbasterol **(99)** where 19-norherbasterol **(100)** resulted from the treatment of herbasterol with either acid or base by a retro-aldol reaction. Four azacyclopropene derivative from the sponge *D. fragilis* were named: azacyclopropene derivatives, (4E)-S-dysidazirine **(101)** and its optical enantiomer dysidazirine (18) (4Z) dysidazirine **(102)** (4E)-antazirine **(103)** and (4Z)-antazirine **(104)** [51]. Meroterpenoids are classes found in *Dysidea* sp. collected from Papua New Guinea. They include avinosol **(105)**, 3′-aminoavarone **(106)**, and 3′-phenethylaminoavarone **(107)**. Their structures were deduced using spectroscopic data analysis. As seen in Table 1, the first naturally occurring meroterpenoid-nucleoside compound, Avinosol, demonstrated anti-invasion activity in a cell-based experiment [52]. Benzothiazole-2-one analog: A novel β_2-adrenoceptor selective agonist, S1319 **(108)** (4-hydroxy-7-[1-(1-hydroxy-2-methylamino) ethyl]-1,3-benzothiazole-2(3*H*)-one) was found from a marine sponge *Dysidea sp*. This is the first eminent example of a β_2-adrenoceptor agonist derived from a marine source [53].

Pharmacological activities

See Table 1.

Discussion

One of the innovative methods for creating and manufacturing pharmaceutical drugs from aquaculture is the use of marine drugs [95]. Marine sponges are considered a drastically important source of active metabolites; however, only a few research papers are present on this topic [96]. Although many different biologically active compounds have been isolated and identified, a review of this field's research demonstrated that not many of those

compounds are being used in clinical trials. This may be due to the difficulty of the successful collection of the concerned sponges in bulk, or the failure of reaching the marine systems themselves [97]. The production of active metabolites is highly variable in marine organisms. Nowadays, due to the significant biological, ecological, and evolutionary ramifications, marine researchers are paying close attention to the origins and effects of those variations. *Dysidea* sp. is common in shallow tropical seas and produce a wide range of substances, including many terpenes, sterols, amino acids, alkaloids, and halogenated secondary metabolites [98]. Many *Dysidea* spp. also are considered the main habitat for several heterotrophic bacteria and photosynthetic cyanobacteria, and these bacteria appear to be able to produce secondary chemicals that are attributed to the host [99]. Some compounds identified from *Dysidea* were namely poly brominated diphenyl ethers (PBDEs) which share structural similarities with hazardous synthetic brominated flame retardants [17]. As seen in Fig. 4, they were mainly found in *D. herbacea, D. chlorea, and D. fragilis* with a variety in their structures indicating that the phenolic natural product molecules isolated from Dysideidae sponges are determined by symbiont genotype. It was noticed that sesquiterpenes represented the major class of compounds, and it was distributed among most of the species. They varied in their carbon skeletons and nitrogenous functionality. Some of the structures were nitrogen-containing metabolites that were occasionally described as sesqui- without any nitrogenous functionality present [100].

Betaines found in *D. herbacea* are intracellular osmoregulators that were isolated before from numerous marine invertebrates [101]. They are established compounds mainly used to treat MAFLD (metabolism-associated fatty liver disease), and cancer as they are methyl-group donors and osmoprotectants. Betaines also reduce oxidative stress and endoplasmic reticulum stress [102].

Diketopiperazines (DKPs) have been found in a variety of sources, including microorganisms (bacteria and fungi), as well as higher organisms (algae, plants, marine sponges, gorgonians, tunicates, and mammals). Chlorinated DKPs are common in marines to boost the bioactivity of the compounds they biosynthesize; they are known to integrate halogens, primarily chlorine and bromine atoms, in their secondary metabolism [103]. They exhibit biological activities, such as cytotoxic, antibacterial, antifungal, antiparasitic, insecticidal, antiviral, antioxidant, anti-inflammatory, antihyperglycemic, and neuroprotective; thus, making them promising drug candidates. Terpenoids are one of the most common compounds isolated from marine organisms so far. In marine sponges, sesterterpenoids (C25) and triterpenoids (C30) are of frequent occurrence, and they show prominent bioactivities [73]. Recently, 15 scalarane-type sesterterpenoids were isolated from many species of *Dysidea*. The biological properties of those compounds were evaluated and were proven to have significant cytotoxic activity [104]. The *Dysidea* sp. is considered a source of many miscellaneous compounds and their degradation products such as ketones, amino acids, azacyclopropene derivatives, and meroterpenoid-nucleosides; thus, it is a potential source for future pharmaceutical drugs.

Future aspects

Because the constant and extensive harvesting of terrestrial plants, pharmaceuticals obtained from them proven to be unreliable and frequently resulted in the re-isolation of known compounds. Academic and pharmaceutical researchers are now concentrating on the sea in quest of novel lead structures from nature. However, a significant challenge is the large-scale synthesis of marine natural compounds for medicinal application; as a result, alternatives that are ethically sound and practical from an economic standpoint are needed [73]. Due to the sophistication of the chemical structure of marine-derived compounds, scientists are now studying and identifying the active pharmacophores that can lead to usable drugs based on a marine prototype through chemical synthesis, modification, degradation, or a combination of those steps. Regarding sponges and other invertebrates, another technique may be utilized in the future including aquaculture of the source organisms to ensure a sustainable supply of the active constituent(s). However, the cultivation of sponges in their natural environment may face some obstacles such as environmental factors like storms or diseases. Endophyte extraction and tissue cultures are among the techniques used recently after intriguing strategies have been done to determine the genuine producers of bioactive chemicals and determine whether they are produced by bacteria or another type of microbial organism, fungi, or cyanobacteria that are known to harbor within the tissues of marine sponges. Finally, the *Dysidea* genus may become one of the most important sponges used in medicine and pharmaceutical industries, but it requires more effort to reach clinical applications.

Conclusion

It has been reported that the sponge *Dysidea* sp. produces chemicals with a range of different structural types and variable pharmacological activities. Sesquiterpenes (the major class), polyketides, steroids, and other bioactive chemicals were reported and identified by their chemical structures in many research papers. The pharmacological properties were found to be of a wide range

including antibacterial, antifungal, cytotoxic, and other properties. This review is done to be a source of enlightenment and motivation for researchers to further perform in clinical investigations on the biological activities of *Dysidea* to gain more knowledge into developing new pharmaceutical agents.

Abbreviations

MAFLD	Metabolism-associated fatty liver disease
DKPs	Diketopiperazines
PBDEs	Polybrominated diphenyl ethers
LI210	Mouse lymphocytic leukemia cell line
IC_{50}	Inhibit a given biological process to half of the maximum and provide a measure of the effectiveness of a compound
ECTA	9α,11α-Epoxycholest-7-ene-3β,5α,6α,19-tetrol 6-Acetate
MRD	Multidrug resistance pump

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