Chemical Biodiversity and Bioactivities of Saponins in Echinodermata with an Emphasis on Sea Cucumbers (Holothuroidea)

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Abstract

Echinoderms are a source of a broad range of secondary metabolites with a large variety of bioactive properties. Although pigment and lipid derivatives are the major groups of bioactive compounds found in crinoids and ophiuroids, saponins represent the most abundant and diverse marine natural products (MNPs) in the phylum Echinodermata. This review is for researchers that are interested in MNPs derived from echinoderms, but with a particular focus on the structural diversity and biological function of saponins. Among the echinoderms, these steroidal compounds are mostly known for and structurally most diverse within sea cucumbers. Through compilation of extensive tables, this review provides a reference book, summarizing not only the major chemical classes of well-known secondary metabolites in the phylum Echinodermata but also further focusing on the presence of bioactive saponins in echinoderms in general and within different sea cucumber species in particular. The final compilation aims to correlate the vast structural diversity of saponins with known biological functions. The here presented data revealed that holothurians, holotoxins, cucumariosides, and echinosids are not only the most abundant saponin compounds in various genera of sea cucumbers but that these saponins can also be used as potential chemotaxonomic markers for different sea cucumber species. By studying the structure-function relationships of triterpene glycosides in echinoderms in general, or in particular within holothurians, the vast structural diversity, taxonomic distribution, and bioactivity of the molecules can be deciphered, which provides an opportunity to focus future research efforts on target species that contain MNPs with novel pharmacological activities.

Keywords

Secondary metabolites · Chemical diversity · Taxonomic markers · Structure-function analysis · Saponins · Echinoderms · Sea cucumber

7.1 Marine Natural Products (MNPs)

Compared to synthesized organic compounds, natural products (NPs) have long been used as efficient and often less harmful sources of drug molecules (Molinski et al. 2009). NPs refer to both primary and secondary metabolites; however, in the past, research on secondary metabolites mostly described ecological interactions of organisms with their environment, the pronounced biological and pharmacological activities, their great chemical diversity, and their higher tendency to interact with other biologically relevant molecules (Croteau et al. 2000).

The marine environment came into the focus of NPs right after technologies for studying marine ecosystems improved. Since the early 1900s, the idea of utilizing marine ecosystems as the potentially largest source for marine natural products (hereafter MNPs) was shaped. Although research on MNPs dates back more than 50 years and more than 32,000 studies related to MNPs have been published (MarineLit; http://pubs.rsc.org/marinlit/), only a few marine-derived compounds resulted in clinical trials (Mayer et al. 2017). That is, from 52 marine invertebrate-derived compounds that reached clinical trials, only seven compounds, isolated from sponges, mollusks, tunicates, and their associated bacteria, have so far

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been approved. Unfortunately, 45 of the total 52 MNPs have been discontinued from clinical trials (Fig. 7.1) due to low production yields and/or high costs.

In this review, we provide an overview on the MNPs reported from echinoderms with an emphasis on MNPs (i.e., particularly triterpene glycosides) reported from shallow water sea cucumbers. While there is extensive literature on the chemistry of MNPs from sessile marine organisms such as sponges, ascidians, and corals, MNP data on slow-moving invertebrates such as echinoderms are much more limited. Up to now, more than 7,000 living echinoderms species, divided into three subphyla and five different classes, have been described (Fig. 7.2). The evolutionary divergence of echinoderms with chordates rather than invertebrates makes their biochemistry and physiology rather similar with vertebrates. They can synthesize vertebrate-type steroids, which regulate their reproductive, growth, and developmental processes (Schoenmakers 1979). Therefore, it can be hypothesized that echinoderms can be promising substitution candidates of the synthetic compounds for producing efficient secondary metabolites helpful for human health. Although several defense mechanisms such as presence of spine, cuvierian tubules (CTs), evisceration, toxic secretion, and unpalatability are generally described for echinoderms and particularly for holothurians, they do not have a significant escape behavior and therefore likely depend on chemical defense strategies, such as triterpene glycosides, to protect themselves against predators (Iyengar and Harvell 2001; Bahrami et al. 2016). Saponins represent a diverse group of triterpene glycosides that have been mainly described from plants and are also one of the major secondary metabolite classes in Echinodermata including holothurians. Saponins are promising MNPs with the capacity to influence physiological and immunological processes and thus have been implicated as bioactive compounds in many ecological studies (Kalinin et al. 1996; Francis et al. 2002). In the following sections, we will discuss in more detail the role of saponins and other bioactive compounds in echinoderms in general, however, with a major focus on sea cucumbers.

7.2 MNPs in Echinoderms

From 28,609 MNPs that have been reported until 2016, more than 35% of the total compounds were isolated from echinoderms. However, the reported chemical diversity of MNPs from echinoderms, compared to other phyla, was not high (Blunt et al. 2018).

Typical reported MNPs derived from echinoderms are sulfated compounds that can be largely classified into two major groups: aromatics and saponins. Among the five classes of echinoderms (Fig. 7.2), aromatic sulfated compounds have only been reported in crinoids and ophiuroids as pigments derived from anthraquinones or naphthoquinones, whereas most of the saponins have been isolated from asteroids, echinoids, and holothuroids (Kornprobst et al. 1998) (Tables 7.1 and 7.2). Among various types of secondary metabolites that have been isolated

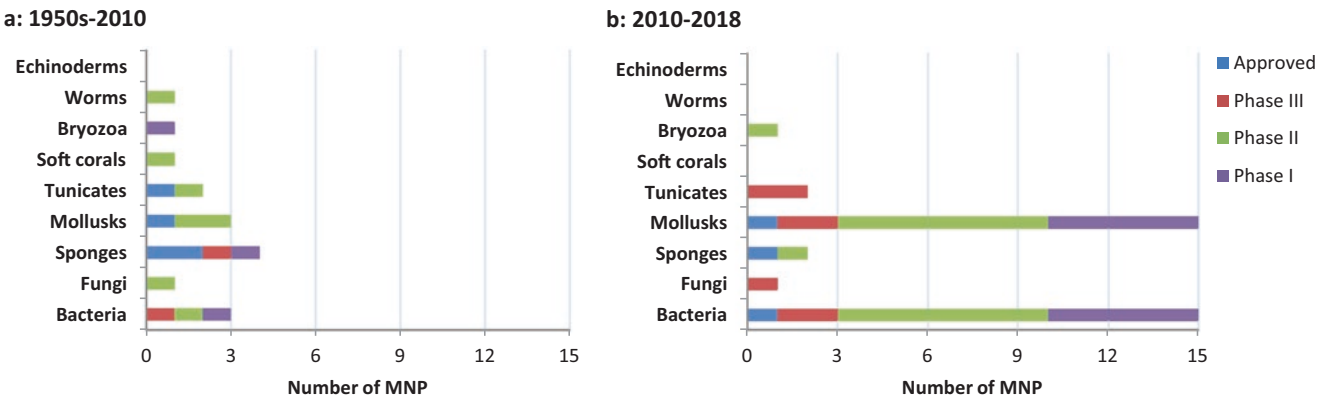

Fig. 7.1 Overview of marine organisms from which MNPs entered the pharmaceutical pipeline (**a**) from 1950s to 2010 and (**b**) from 2010 to 2018. (Compiled with data from Mayer and Hamann 2002; Mayer et al. 2017; http://marinepharmacology.midwestern.edu)

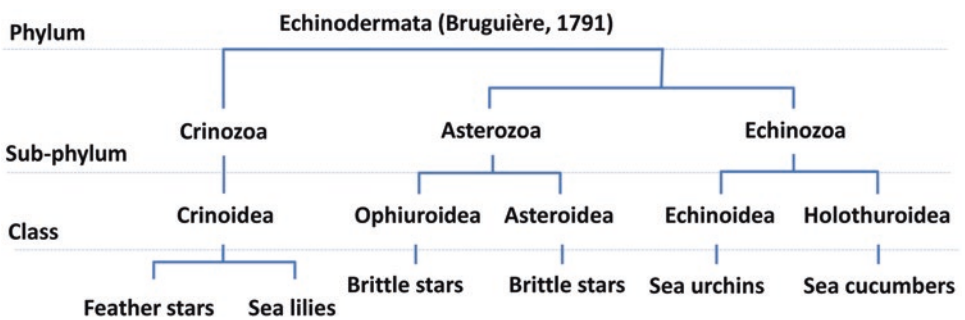

Fig. 7.2 Phylogenetic tree for the phylum Echinodermata (modified after Telford et al. 2014)

Table 7.1 Classes of echinoderms, major classes of secondary metabolites, examples of compounds, their bioactivity, and example species for which the compounds have been reported

	Major classes of secondary metabolites	Examples of bioactive compounds	Biological activity	Example of organisms	References
Crinoids: Lipids, pigments, polyketides	Polyketides	Rhodoptilometrin, crinemodin	Antipredatory	**Comanthus bennetti*	Rideout et al. (1979)
	Lipids	Ganglioside, cerebrosides	n.d.	**Comanthina schlegelii*	Inagaki et al. (2007)
	Naphthopyrones	Naphthopyrones comaparvin	Anti-inflammatory	*Comanthus parvicirrus*	Karin et al. (2004), Folmer et al. (2009), Chovolou et al. (2011), and Chen et al. (2014)
	Anthraquinoid pigments	Gymnochrome D	Antiviral	**Gymnocrinus richeri*	Laille et al. (1998)
Asteroids: Steroidal derivatives of cholesterol, fatty acids, ceramides, and few alkaloids and proteins	Lipids	Hexadecanoic acid	Antifouling	*Linckia laevigata*	Guenther et al. (2009)
	Lipids	Sphingolipids	n.d.	*Ophidiaster ophidianus*	Jin et al. (1994)
	Asterosaponins	Thornasteroside A	Antitumor	*Asteropsis carinifera*	Malyarenko et al. (2012)
	Fatty acids	Eicosanoic acid	n.d.	*Culcita novaeguineae*	Bruno et al. (1992) and Inagaki (2008)
	Protein	Ciguatoxins	n.d.	*Marthasterias glacialis*	Silva et al. (2015)
	Polyhydroxysteroids	Laeviusculosides	Hemolytic, cytotoxic activity	*Henricia leviuscula*	Ivanchina et al. (2006) and Fedorov et al. (2008)
Ophiuroids: Carotenoids, gangliosides, brominated indoles, phenyl propanoids, terpenes, steroids	Steroidal glycosides	Steroidal glycosides	Antiviral	*Ophiarachna incrassata*	D'Auria et al. (1993)
	Steroidal compound	Polyhydroxysterols	Antiviral	*Astrotoma agassizii*	Comin et al. (1999)
	Terpene	2,3-Dimethyl butenolide	Antitumor	*Ophiomastix mixta*	Lee et al. (2007)
	Carotenoid	Ophioxanthin	Antioxidant	*Ophioderma longicauda*	D'Auria et al. (1985)
Echinoids: Protein, polysaccharides, lipid, pigments	Naphthoquinoid pigment	Echinochrome A	Antioxidant, antimicrobial, anti-inflammatory, antitoxic agents	**Anthocidaris crassispina*	Berdyshev et al. (2007) and Jeong et al. (2014)
	Peptides	Strongylostatin	Anticancer	*Strongylocentrotus droebachiensis*	Pettit et al. (1981)
		Strongylocins	Antimicrobial	*Strongylocentrotus droebachiensis*	Li et al. (2008)
	Polysaccharide	Sulfated fucan	Anticoagulant	*Lytechinus variegatus*	Pereira et al. (1999)
	Steroidal compounds	n.d.	Anticancer	*Diadema savignyi*	Thao et al. (2015a)
	Ganglioside	DSG-A	Neuritogenic	*Diadema setosum*	Yamada et al. (2008)

(continued)

Table 7.1 (continued)

	Major classes of secondary metabolites	Examples of bioactive compounds	Biological activity	Example of organisms	References
Holothuroids: Triterpene glycosides, peptides, polysaccharides, lipids	Triterpene glycoside	Holothurins (A–B)	Antifungal, anticancer, ichthyotoxic	*Holothuria atra, Holothuria fuscocinerea*	Yamanouchi (1955), Kobayashi et al. (1991), Popov et al. (1994), and Zhang et al. (2006d)
	Triterpene glycoside	Echinoside A	Antifungal	*Actinopyga echinites*	Kitagawa et al. (1985)
	Triterpene glycoside	Holotoxin A–F	Anticancer, antifungal, antiprotozoa	*Apostichopus japonicus*	Kitagawa et al. (1976), Anisimov et al. (1983), Maltsev et al. (1985), and Wang et al. (2012)
	Triterpene glycosides	Holotoxin	Antifungal	*S. japonicus*	Yano et al. (2013)
	Polysaccharides	Glucosamine, Galactosamine	Antihyperlipidemic, antioxidant	*A. japonicus*	Liu et al. (2012)
	Sulfated polysaccharides	FucCS, GAGs	Anticoagulant, antithrombin, antiparasitic	*Ludwigothurea grisea*	Mourão et al. (1998), Borsig et al. (2007), and Marques et al. (2016)
	Sulfated polysaccharides	FucCS	Anticoagulant, antithrombin, antihyperglycemic, antiviral, insulin-sensitizing	*Thelenota ananas, Cucumaria frondosa*	Borsig et al. (2007), Huang et al. (2013), and Hu et al. (2014a)
	Sulfated polysaccharides	FucCS	Anticoagulant, antiparasitic	*Isostichopus badionotus*	Marques et al. (2016)
	Sulfated polysaccharides	GAGs	Antihyperlipidemic	**Metriatyla scabra*	Liu et al. (2002)
	Fatty acid	EPA-enriched PL, 12-MTA, ODAs	Antioxidant, antihyperglycemic, anticancer, antihyperlipidemic	*C. frondosa, Stichopus japonicus*	Yang et al. (2003), Nguyen et al. 2011, Hu et al. (2014b), Wu et al. (2014), and Ku et al. (2015)
	Lipid	Cerebrosides, galactocerebrosides, AMC-2	Anticancer, antihyperlipidemic	**Stichopus variegatus, Acaudina molpadioides, Bohadschia argus*	Sugawara et al. (2006), Ikeda et al. (2009), Zhang et al. (2012), and Du et al. (2015)
	Sphingolipid	Cerebroside	Antioxidant	*S. japonicus, Acaudina molpadioides*	Duan et al. (2016) and Xu et al. (2011)
	Lysophospholipid	LPC, L-PAF	Anti-inflammatory	*Holothuria atra*	Nishikawa et al. (2015)
	Peptide	Phenoloxidase, lysozyme	Antimicrobial	*C. frondosa*	Beauregard et al. (2001)
	Peptide	ACE inhibitory peptide	Antihypertension	*Acaudina molpadioides*	Zhao et al. (2009)
	Peptide	T-antigen-binding lectin	Antibacterial	*Holothuria scabra*	Gowda et al. (2008)
	Phenolic compounds	n.d.	Anti-inflammatory	*S. japonicus*	Song et al. (2016)

(continued)

Table 7.1 (continued)

	Major classes of secondary metabolites	Examples of bioactive compounds	Biological activity	Example of organisms	References
	Phenolic compounds	(Z)2,3-DPAN	Anticancer	*Holothuria parva*	Amidi et al. (2017)
	Pigments	Carotenoids	Antioxidant	*Holothuria atra*	Esmat et al. (2013)
	Pigments	β-carotene, echinenone, canthaxanthin, etc.	Antioxidant	*Plesiocolochirus minaeus*	Maoka et al. (2015)
	Sulfated alkene	2,6-DMHS, OS, DS	Antibacterial, antifungal	*A. japonicus*	La et al. (2012)
	Mucopolysaccharide	SJAMP	Antitumor, immunomodulatory effect	*S. japonicus*	Song et al. (2013)
	Glycolipid/ Sphingolipid	2,6-DMHS, OS, DS	Anticancer	*A. japonicus*	La et al. (2012)
	Saponin	Frondanol A_5	Anticancer	*C. frondosa*	Janakiram et al. (2010)and Jia et al. (2016)
	Saponin	n.d.	Antihyperlipidemic	*Pearsonothuria graeffei*	Hu et al. (2010) and Wu et al. (2015)
	Monosulfated triterpene glycosides	Cumaside	Radioprotective	*Cucumaria japonica*	Aminin et al. (2011)

n.d. not defined, *EPA-enriched PL* eicosapentaenoic acid-enriched phospholipids, *FucCS* fucosylated chondroitin sulfate, *GAGs* glycosaminoglycan, *2,6-DMHS* 2,6-dimethylheptyl sulfate, *OS* octyl sulfate, *DS* decyl sulfate, *ACE* angiotensin I-converting enzyme, *LPC* lysophosphatidylcholine, *L-PAF* lyso-platelet activating factor, *SCEA-F* ethyl acetate solvent fraction of sea cucumber, *EPA-enriched PC* eicosapentaenoic acid-enriched phosphatidylcholine lipids, *12-MTA* 12-methyltetradecanoic acid, *(Z)2,3-DPAN* (Z)-2,3-diphenylacrylonitrile, *SJAMP stichopus japonicus* acid mucopolysaccharide, *ODAs* 7(Z) octadecenoic acid, and 7(Z),10(Z)-octadecadienoic acid
*Based on WoRMS (2019), the accepted names changed from: *Metriatyla scabra to Holothuria scabra; Comanthus bennetti to Anneissia bennetti; Comanthina schlegelii to Comaster schlegelii; Gymnocrinus richeri to Neogymnocrinus richeri; Anthocidaris crassispina to Heliocidaris crassispina; Stichopus variegatus to Stichopus horrens*

from echinoderms, saponins are the most abundant. Compounds were derived from mainly two classes (i.e., Asteroidea and Holothuroidea) (Haug et al. 2002), which will be discussed in more detail in Sect. 7.3.

7.2.1 Crinoids (Feather Stars and Sea Lilies)

The most primitive form of current echinoderms are the crinoids (Karleskint et al. 2010). Sea lilies are, unlike feather stars, sessile and are found mainly in depths >100 m, whereas feather stars inhabit coral reefs from the intertidal to the deep-sea oceans. Moreover, feather stars are physically able to escape from predators by crawling, swimming, or hiding between corals or rocks (Ruppert et al. 2004; Karleskint et al. 2010). Furthermore, crinoids use other physical and chemical defense mechanisms to protect them against fish predators. For example, crinoids use spike-like pinnules as well as toxic chemical compounds such as polyketide derivatives and oxidized quinones that also give them their colorful appearance (Kenta et al. 2015; Feng et al. 2017). According to WoRMS[1] 2017, although they consist of nearly 700 species worldwide, until now only a few studies examined their bioactive compounds. According to the MarinLit database (2018), only 25 marine species from 16 different genera of crinoids have so far been screened for novel MNPs (Feng et al. 2017) (Table 7.1).

7.2.2 Asteroids (Sea Stars)

This class of echinoderms is, with over 1500 species, widely distributed and thus plays important ecological roles. Asteroids are opportunistic feeders, and species such as the temperate Ochre sea star *Pisaster ochraceus* and the tropical coral-eating crown of thorn sea star *Acanthaster planci* are keystone species (Paine 1969). Asteroids are known to use both physical and chemical defense mechanisms. Autotomy (i.e., found in *Evasterias troschelii* and *Pycnopodia helianthoides*), spines, modified tube feet called "pedicellaria," camouflage, quick locomotion, and shedding have been reported as physical defenses (Bryan et al. 1997; Candia Carnevali and Bonasoro 2001). However, some species such as the sea star *Pteraster tesselatus* rely to a great extent on their mucus as chemical defense (Nance and Braithwaite

[1]World Register of Marine Species.

Table 7.2 Steroidal compounds reported from echinoderms, except Holothuroids, and (if reported) their biological activities (Holothuroids see Table 7.3)

Class	Family	Species	Isolated compounds	Biological activity	References
Crinoids	Hemicrinidea	*Neogymnocrinus richeri*	Several steroids	n.d.	De Riccardis et al. (1991)
Asteroids	Asteriidae	*Asterias amurensis*	Thornasteroside A, versicosides A–C, and asteronylpentaglycoside sulfate, anasteroside B	n.d.	Hwang et al. (2011, 2014)
			Crude saponin	Insecticide and repellant activity	Park et al. (2009)
			Asterosides A–D, glycoside B, asterosaponins	n.d.	Riccio et al. (1988)
			Asterosaponin-4	Cytotoxic	Okano et al. (1985)
			Asterosaponin A, A_4	Antitumor	Ikegami et al. (1973)
		Asterias vulgaris	13 steroidal compounds	n.d.	Findlay and Agarwal (1983)
		Asterias forbesi	Forbeside D	n.d.	Findlay and He (1991)
			Forbesides A–B	Anti-inflammatory, Antiviral	Findlay et al. (1987)
			Forbesides C–E, E_1-E_3, F-H, L	n.d.	Findlay et al. (1989), Findlay and He (1991), D'Auria et al. (1993), and Jiang et al. (1993)
			Forbeside H	n.d.	Findlay et al. (1992)
		Asterias rubens	Ruberosides A–F	n.d.	Sandvoss et al. (2000, 2003)
		Asterias rathbuni	Rathbuniosides R_1-R_2	Cytotoxic	Prokof'eva et al. (2003)
		Anasterias minuta	Minutosides A, B	Antifungal	Chludil et al. (2002b)
			Anasterosides A–B, versicoside A	Antifungal	Chludil et al. (2002b)
		Asterias rollestoni	Amurensoside, forbeside		Zhang et al. (2013)
		Aphelasterias japonica	Aphelasteroside F	Inhibition of cell proliferation	Popov et al. (2016)
			Ophidianoside F	n.d.	Ivanchina et al. (2005)
			Aphelasteroside C (1), cheliferoside L_1 (2),3-O-sulfoasterone (3), forbeside E_3 (4), and 3-O-sulfothornasterol A (5) aphelaketotriol (6)	Hemolytic activity except compound (3)	Ivanchina et al. (2000)
		Leptasterias hylodes	Polyhydroxylated steroids	Antibacterial, hemolytic activity	Levina et al. (2010)
			Hylodoside A, novaeguinoside Y	Hemolytic activity	Levina et al. (2010)
		Leptasterias ochotensis	Leptasteriosides A–F	Anticancer	Malyarenko et al. (2014)
		Diplasterias brucei	Diplasteriosides A, B	Anticancer	Ivanchina et al. (2011)
		Coscinasterias tenuispina	Tenuispinosides A–C, coscinasteroside A–F	n.d.	Riccio et al. (1986d)
		Distolasterias nipon	Nipoglycosides A–D, versicoside A, and thornasteroside A	n.d.	Minale et al. (1995)
			Distolasterosides D_1–D_3	Neurogenic and neuroprotective effect	Palyanova et al. (2013)
		Distolasterias elegans	Pycnopodioside C	n.d.	Andriyashchenko et al. (1996)
		Lethasterias fusca	Lethasterioside A	Anticancer	Ivanchina et al. (2012)
		Lysastrosoma anthosticta	Lysaketotriol and iysaketodiol	Immunomodulatory activities	Levina et al. (2009)

(continued)

Table 7.2 (continued)

Class	Family	Species	Isolated compounds	Biological activity	References
			Luridosides A, marthasterone, marthasteroside, pyncopodioside C	n.d.	Levina et al. (2001)
		Marthasterias glacialis	Thornasteroside A, maculatoside A_1, A_2, B–C	n.d.	Bruno et al. (1984) and Minale et al. (1985)
	Oreasteridae	*Pentaceraster gracilis*	Pentacerosides A and B, maculatoside	Maculatoside: cytotoxic	Vien et al. (2017)
		[a]*Anthenea chinensis*	Anthenoside A, E, G, H, I, J, K	Antitumor	Ma et al. (2009a, 2010)
		Culcita novaeguineae	Culcinosides A–D	Cytotoxic	Lu et al. (2018)
			Novaeguinosides I,II, A–E, regularoside B	Antitumor	Tang et al. (2005) and Ngoan et al. (2015)
			Sodium (20R,24S)-6α-O-(4-O-sodiumsulfato-β-d-quinovopyranosyl)-5α-cholest-9(11)-en-3β,24-diol 3-sulfate	Anticancer	Ma et al. (2009b)
			Sodium (20R,24S)-6α-O-[3-O-methyl-β-d-quinovopyranosyl-(1→2)-β-d-xylopyranosyl-(1→3)-β-d-glucopyranosyl]-5α-cholest-9(11)-en-3β,24-diol 3-sulfate	Anticancer	Ma et al. (2009b)
			Galactocerebroside	n.d.	Inagaki et al. (2006)
			Polyhydroxylated steroids	Antibacterial, hemolytic activity	Levina et al. (2010)
			Hylodoside A, novaeguinoside Y	Hemolytic activity	Levina et al. (2010)
			Culcitoside C_2–C_3	Hemolytic activity, cytotoxic	Prokof'eva et al. (2003)
			Culcitoside C_1–C_8	n.d.	Kicha et al. (1985, 1986) and Iorizzi et al. (1991)
			Regularosides A–B, thornasteroside A, marthasteroside A_1	Cytotoxic	Tang et al. (2006)
			Asterosaponin 1, novaeguinosides I and II	Antitumor	Cheng et al. (2006) and Tang et al. (2009)
		Protoreaster nodosus	Nodososide	Anti-inflammatory, cytotoxic	Riccio et al. (1982b) and Thao et al. (2015b)
			Ganglioside, galactocerebroside, ganglioside PNG-2A	n.d.	Pan et al. (2010, 2012) and Kenta et al. (2015)
			Three steroids	n.d.	Riccio et al. (1982b) and Minale et al. (1984b)
			Protoreasteroside	n.d.	Riccio et al. (1985d)
		Pentaceraster alveolatus	Protoreasteroside	n.d.	Riccio et al. (1985d)
		Halityle regularis	Halityloside A–F, halityloside H	n.d.	Iorizzi et al. (1986)
			Regularosides A, B, thornasteroside A	n.d.	Riccio et al. (1986c)
		Oreaster reticulatus	Sulfated glycosides analog of nodososide	n.d.	De Correa et al. (1985)
			Reticulatosides A, B, ophidianoside F	n.d.	Iorizzi et al. (1995)
		Choriaster granulatus	Granulatosides A–E	D–E: Immunomodulatory effect	Pizza et al. (1985a) and Ivanchina et al. (2017, 2018)

(continued)

Table 7.2 (continued)

Class	Family	Species	Isolated compounds	Biological activity	References
	Ophidiasteridae	*Hacelia attenuata*	Nodososide, attenuatosides A-I, B-I, B-II, and C, polyhydroxysteroids	n.d.	Minale et al. (1983)
			Attenuatosides S-I–S-III, S-D, thornasteroid	n.d.	Minale et al. (1984a)
			Ophidianosides B, C, F	n.d.	Riccio et al. (1985c)
		Linckia laevigata	Thornasteroside A, marthasteroside A_1, ophidianoside F, maculatoside, laevigatoside	n.d.	Riccio et al. (1985b)
			Granulatoside A	Neuritogenic activity	Qi et al. (2006)
			Nodososide	n.d.	Minale et al. (1984c)
			Linckosides A–Q	Neuritogenic activity	Qi et al. (2002, 2004) and Han et al. (2006, 2007a)
			Linckosides L_1–L_7, echinasteroside C	Neuritogenic activity, cytotoxic	Kicha et al. (2007a, b, c)
		Ophidiaster ophidianus	Ophidianoside B–F	n.d.	Riccio et al. (1985c)
		Certonardoa semiregularis	Certonardoside A–J, halytoside D	Antiviral	Wang et al. (2002)
			Certonardoside K-N, culcitoside C_6	Cytotoxic, antibacterial	Wang et al. (2003)
			Certonardosterol Q_1–Q_7, B_2–B_4, A_2–A_4, D_2–D_5, H_3, H_4, E_2, E_3, P_1, O_1	Cytotoxic, antitumor	Wang et al. (2004a, b)
			Certonardoside B_2, B_3, P_1, P_2, O_1, J_2, J_3, I_2, I_3, H_2	Cytotoxic, antitumor	Wang et al. (2004a, 2005)
		Nardoa gomophia	Halityloside A, B, D, E, H, I, marthasteroside A_1, thornasteroide A, and 2 polyhydroxysteroids	n.d.	Riccio et al. (1986b)
		Nardoa novaecaledonia	Halityloside A, B, D	n.d.	Riccio et al. (1986b)
	Asterinidae	*Patiria pectinifera*	Polyhydroxysteroids	Cytotoxic.	Peng et al. (2010)
			Cucumarioside F_1, F_2	Indicative of trophic marker	Popov et al. (2014)
			Asterosaponin P_1,P_2, polyhydroxysteroids	Asterosaponin P1: neurogenic and neuroprotective effect	Kicha et al. (1983, 2000, 2004) and Palyanova et al. (2013)
			Pectinoside A	Immunological activity	Kawase et al. (2016)
		Asterina pectinifera	Pectiniosides A–J, acanthaglycciside C	Cytotoxic	Dubois et al. (1988), Honda et al. (1990), Jiang and Schmidt (1992), and Li et al. (2013)
		Asterina batheri	Astebatheriosides A–D	Astebatheriosides B-D: anti-inflammatory	Thao et al. (2013)
		Patiria miniata	Patiriosides A–G	Antitumor	Dubois et al. (1988), and D'Auria et al. (1990)

(continued)

Table 7.2 (continued)

Class	Family	Species	Isolated compounds	Biological activity	References
	Asteropectinidae	*Astropecten polyacanthus*	Astropectenols A, C, D	Antiparasitic	Thao et al. (2013, 2014)
		Astropecten monacanthus	Astrosteriosides A, D, C	Anti-inflammatory, anticancer	Thao et al. (2013, 2014) and Dai and Yu (2015)
		Craspidaster hesperus	Asterosaponin	n.d.	Wen et al. (2004)
		Psilaster cassiope	Psilasteroside	Cytotoxic	De Marino et al. (2003)
		Astropecten latespinosus	Latespinosides A–D	Weak-cytotoxic	Higuchi et al. (1996)
	Echinasteridae	*Henricia leviuscula*	Laevisculoside, laevisculoside A–J, H_2 sanguinosides A–B	Hemolytic activity	Kalinovskii et al. (2004), and Ivanchina et al. (2006)
			Laevisculoside G	Anticancer	Fedorov et al. (2008)
			Sanguinoside C	Cytotoxic	Levina et al. (2003)
		Henricia sanguinolenta	Laevisculoside, sanguinoside A–B	n.d.	Kalinovskii et al. (2004)
			Sanguinoside C	Cytotoxic	Levina et al. (2003)
		Henricia derjugini	Henricioside H_1–H_3, hexaol	n.d.	Ivanchina et al. (2004)
			Henricioside H_1, levisculoside G	Antifungal	Kaluzhskiy et al. (2017)
		Henricia sp.	Henriciosides H_1–H_3	n.d.	Kicha et al. (1993)
		Henricia downeyae	Asterosaponins	Antibacterial, antifungal, feeding deterrent	Palagiano et al. (1996)
		Echinaster brasiliensis	Brasilienoside, desulfated dihydro-echinasteroside A, echinasteroside B–G, marthasteroside A_1	n.d.	Iorizzi et al. (1993)
		Echinaster sepositus	22,23-epoxysteroidal (cyclic) glycosides	n.d.	Riccio et al. (1981), and Minale et al. (1997)
			Amurasterol, asterosterol	n.d.	De Simone et al. (1980)
			Sepositoside A	Cytotoxic	De Simone et al. (1981)
			Echinasterosides A, B_1, B_2, laeviusculosides C, I	n.d.	Zollo et al. (1985), Levina et al. (1987), and Iorizzi et al. (1993)
		Echinaster luzonicus	Sepositoside A, luzonicosides A, D	Cytotoxic, anticancer	De Simone et al. (1981), Riccio et al. (1982a), and Malyarenko et al. (2017)
	Stichasteridae	*Neosmilaster georgianus*	Santiagoside	n.d.	Vázquez et al. (1992)
		Cosmasterias lurida	Cosmasterosides A–D, forbeside H	n.d.	Roccatagliata et al. (1994)
			Luridosides A–B	n.d.	Maier et al. (1993)
	Asteropseidae	*Asteropsis carinifera*	Asteropsiside A, regularoside A, and thornasteroside A	Antitumor	Malyarenko et al. (2012)
			Cariniferosides A–F	No cytotoxicity	Malyarenko et al. (2011)
			Polyhydroxysteroids	n.d.	Malyarenko et al. (2010)

(continued)

Table 7.2 (continued)

Class	Family	Species	Isolated compounds	Biological activity	References
	Archasteridae	*Archaster typicus*	Five steroids	Anticancer	Yang et al. (2011)
			Archasterosides A–C	Anticancer	Kicha et al. (2010a, b)
	Luidiidae	*Luidia maculata*	Thornasteroside A, maculatosides A–C, A_2	Anticancer	Minale et al. (1985)
		Luidia quinaria	Thornasterol	n.d.	Andriyashchenko et al. (1996)
			Luidiaquinoside, psilasteroside	Cytotoxic	De Marino et al. (2003)
	Acanthasteridae	*Acanthaster planci*	Thornasterols A and B	Cytotoxic	Kitagawa and Kobayashi (1977, 1978)
			Acanthaglycoside B–F, marthasteroside A_1, and versicoside A–B	n.d.	Itakura and Komori (1986)
			5-Deoxyisonodososide, isonodososide	Cytotoxic	Pizza et al. (1985b)
			Nodososide	n.d.	Minale et al. (1984c)
	Goniopectinidae	*Goniopecten demonstrans*	Goniopectenosides A–C	Antifouling	De Marino et al. (2000)
		Hippasteria phrygiana	Hippasteriosides A–D	Hippasterioside D: anticancer	Kicha et al. (2011)
			Phrygiasterol (1), phrygioside B (2), borealoside C (3)	(1,2): Anticancer	Levina et al. (2004, 2005)
	Goniasteridae	*Mediaster murrayi*	Mediasteroside M_1	Anticancer	Prokof'eva et al. 2003
		Ceramaster patagonicus	Ceramasterosides C_1–C_3	Cytotoxic	Prokof'eva et al. (2003)
	Heliasteridae	*Heliaster helianthus*	Helianthoside	Cytotoxic	Vázquez et al. 1993
		Labidiaster annulatus	Labiasteroside A	n.d.	de Vivar et al. (1999)
	Solarestridae	[b]*Solaster borealis*	Solasteroside A, borealosides A–D, amurenoside B	Cytotoxic	Iorizzi et al. (1992)
	Zoroasteridae	*Myxoderma platyacanthum*	Myxodermoside A and 9 polyhydroxysteroids	n.d.	Finamore et al. (1991)
	Brisingidae	*Novodinia antillensis*	steroidal saponins: Sch 725737 and Sch 725739	Cytotoxic	Yang et al. (2007)
Ophiuroids	Ophiocomidae	[c]*Ophiocoma dentata*	Sulfated polyhydroxysterols	Antiviral	D'Auria et al. (1993)
		[d]*Ophiarthrum elegans*	Sulfated polyhydroxysterols	Antiviral	D'Auria et al. (1987, 1993)
		Ophiocoma erinaceus	n.d.	Hemolytic activity	Amini et al. (2014)
	Ophiopholidae	*Ophiopholis aculeata*	Sulfated polyhydroxysterols	Cytotoxic and hemolytic activity	Aminin et al. (1995)
	Ophiomyxidae	*Ophiarachna incrassata*	Sulfated polyhydroxysterols	Antiviral	D'Auria et al. (1987, 1993)
	Hemieuryalidae	*Ophioplocus januarii*	Sulfated steroids	Antiviral	Roccatagliata et al. (1996)
	Gorgonocephalidea	*Astrotoma agassizii*	Polyhydroxysterols	Antiviral	Comin et al. (1999)
	Ophiodermatidae	*Ophioderma longicauda*	Longicaudosides A–B	n.d.	Riccio et al. (1985a, 1986a)
Echinoids	Diadematidae	*Diadema savignyi*	Steroidal compounds	Anticancer	Thao et al. (2015a)
	Toxopneustidae	*Tripneustes gratilla*	Epidioxysterol	Cytotoxic	Liu et al. (2011)

[a]The accepted name changed from "*Anthenea chinesis*" to "*Anthenea pentagonula*"
[b]The accepted name changed from "*Solaster borealis*" to "*Crossaster borealis*"
[c]The accepted name changed from "*Ophiocoma dentata*" to "*Breviturma dentata*"
[d]The accepted name changed from "*Ophiarthrum elegans*" to "*Ophiomastix elegans*"

1979). Based on the hypothesis that saponins and saponin-like compounds produce various sugars upon hydrolysis (Fieser and Fieser 1956), Ward (1960) proposed that mucous-like compounds secreted from *Pteraster tessellates* have a saponin or saponin-like nature. Starfishes produce a wide range of MNPs (Table 7.2), which are largely described as lipid-like or lipid soluble molecules. Asteroids produce various steroidal derivatives, fatty acids, ceramides, and few alkaloids to either defend themselves or communicate (Table 7.1). Some of the latter compounds have been reported to possess pharmacological activities (Maier, 2008). After sea cucumbers, this group of echinoderms has also been reported to produce a large number of saponins, which have been isolated from different organs (i.e., stomach, arm, gonads, and digestive system) and possess various roles in digestion (Garneau et al. 1989; Demeyer et al. 2014), reproduction (Mackie et al. 1977) and the defense against potential predators (Harvey et al. 1987). Assessing the isolated steroidal glycosides from 1973 to 2016 revealed that most of the MNP studies on sea stars had focused on the families Asteroidea (26%), Echinasteridae (17%), Oreasteridae (16%), and Ophidiasteridae (13%; Table 7.2 and references therein).

The glycoside compounds of starfish are classified into three main groups of steroidal glycosides: asterosaponin, polyhydroxylated glycosides, and macrocyclic glycosides (Kicha et al. 2001; Maier 2008; Demeyer et al. 2014). Although steroidal glycosides are the characteristics of asteroids, triterpene glycosides have also been isolated from starfishes such as *Asterias rollestoni* (Zhan et al. 2006) and *Patiria pectinifera* (Popov et al. 2014). The isolated saponins from *A. rollestoni* (rollentosides A–B) have a similar aglycone and carbohydrate moiety than those observed in some sea cucumber species (Popov et al. 2014). Given the similar structures of rollentoside B (Zhan et al. 2006) and cucumarioside A_{15} that have been extracted from the sea cucumber *Eupentacta fraudatrix* (Silchenko et al. 2012a), it has been argued that the starfish fed on the sea cucumber (Popov et al. 2014; Fig. 7.3). Furthermore, it seems that *A. rollestoni* is

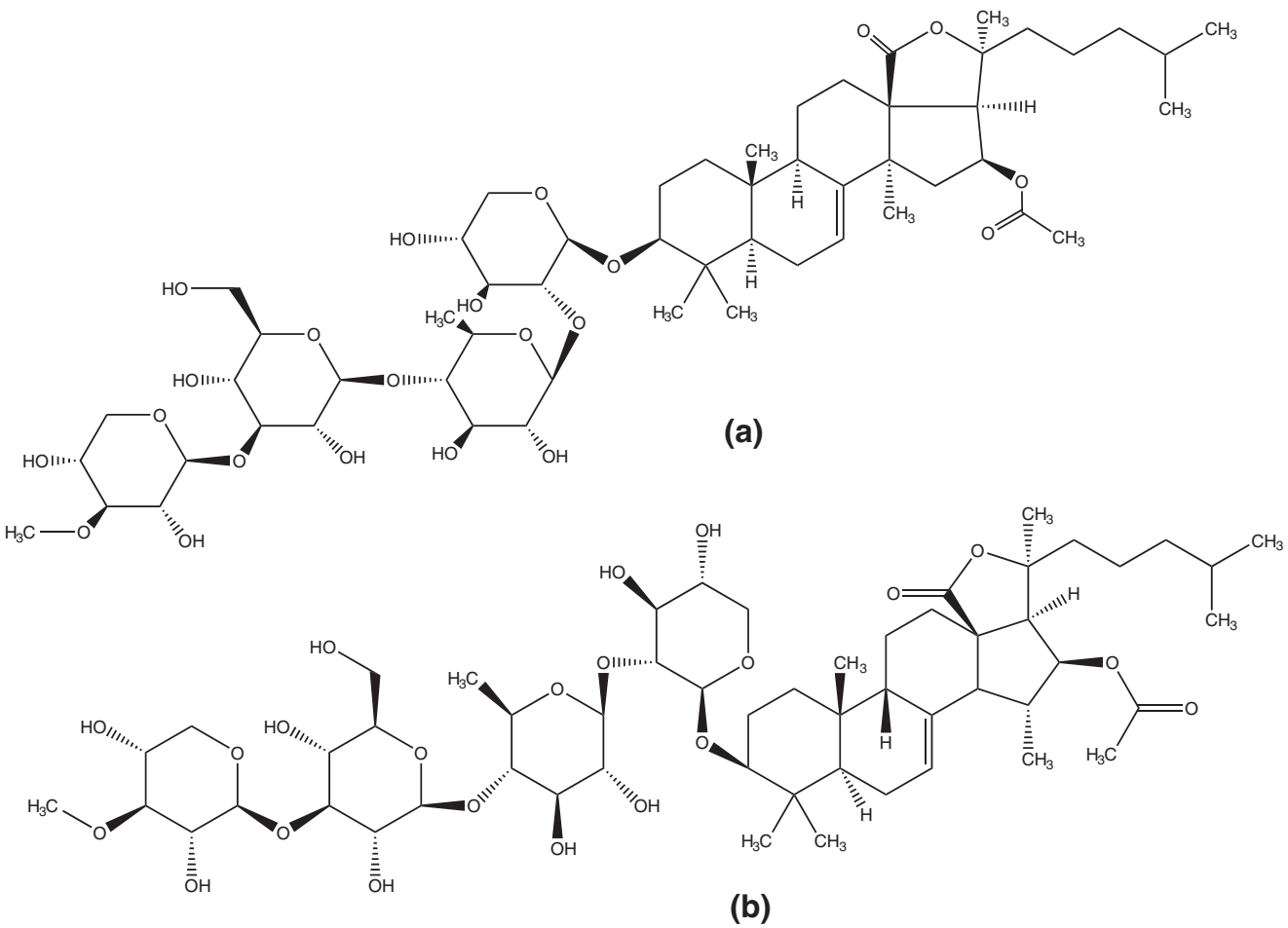

Fig. 7.3 (**a**) Rollentoside B isolated from *Asterias rollestoni* and (**b**) Cucumarioside A_{15} isolated from *Eupentacta fraudatrix* with similar chemical formula of $C_{55}H_{88}O_{22}$ (produced with ChemDraw, version 16.0.1.4 (77))

able to digest and also to accumulate the toxic triterpene glycosides that were originally derived from sea cucumbers.

7.2.3 Ophiuroids (Brittle Stars)

With over 2000 species, brittle stars are the largest group of echinoderms (Hickman et al. 2001). These organisms are widely distributed, and their feeding behavior can be suspension feeding, deposit feeding, and/or predation (Stöhr et al. 2012). Although brittle stars have numerous physical defense mechanisms such as fast locomotion, a quick removal of their extremities, and the ability to hide under rocks and crevices, some species still rely on chemical defenses. However, based on the MarineLit database, to this day only a few studies focused on ophiuroids. Nuzzo et al. (2017) mentioned that several classes of secondary metabolites such as carotenoids, gangliosides, brominated indoles, phenylpropanoids, several groups of terpenes, and steroids have been isolated from brittle stars (Table 7.1). The presence of sulfated steroids in starfish (see Sect. 7.3) and brittle stars is an indicator of the phylogenetically close relation between these two classes of echinoderms (Levina et al. 1996, 2007).

7.2.4 Echinoids (Sea Urchins)

Sea urchins, the living representative of echinoids, are free-moving echinoderms (Clemente et al. 2013). They typically have physical defense mechanisms such as fused skeleton plates, spines, and pedicellaria for pinching or capturing prey (Jangoux 1984). Some families such as Diadematidae, Echinothuriidae, and Toxopneustidae contain venoms (Thiel and Watling 2015). The main MNPs of sea urchins are proteins, polysaccharides, and pigments, which are located in the spines, testes, gonads, and/or pedicellaria (Shang et al. 2014; Jiao et al. 2015). Studies on their MNPs have mainly focused on proteins derived from naphthoquinone pigments that showed antibacterial, antioxidant, and anti-inflammatory activities. Few studies focused on steroidal components of sea urchins (Table 7.2), with the exception of *Tripneustes gratilla* (Liu et al., 2011) and *Diadema savignyi* (Thao et al. 2015a), from which several steroidal constituents had been described.

7.2.5 Holothuroids (Sea Cucumbers)

Sea cucumbers have been recognized as an interesting source of MNPs, since they are already used as traditional food and medicine source in Asian countries (i.e., healing wounds, eczema, arthritis, impotence; Ridzwan 2007; Althunibat et al. 2013). The enriched nutrition profile of sea cucumbers and their high protein, low sugar, and cholesterol-free content make holothurians a valuable food source, especially for people who suffer from hyperlipidemia (Wen et al. 2010; Bordbar et al. 2011). To date, antibacterial (Ghanbari et al. 2012; Soliman et al. 2016), antifungal (Ghannoum and Rice 1999; Soliman et al. 2016), antiviral (Mayer and Hamann 2002), antitumor and anticancer (Anisimov et al. 1973; Wu et al. 2007a; Janakiram et al. 2015; Fedorov et al. 2016), anti-schistosomal (Mona et al. 2012), and anti-inflammatory (Song et al. 2016) activities are the reported bioactive effects that were obtained from various classes of sea cucumber-derived secondary metabolites. Although a wide range of chemical classes from sea cucumbers such as peptides (Zhao et al. 2009; Song et al. 2016), polysaccharides (Liu et al. 2012; Marques et al. 2016), glycosphingolipids (Sugawara et al. 2006), polyunsaturated fatty acids (Yang et al. 2003; Hu et al. 2014b), and ceramides and gangliosides (Ikeda et al. 2009) were studied (Table 7.2), only a few products reached preclinical trials (Mayer et al. 2010).

7.3 Saponins in Echinoderms

The major group of bioactive compounds that are responsible for the biological activities of echinoderms are glycosides (Bhakuni and Rawat 2005; Dong et al. 2011). Saponins are common compounds that have been isolated from various terrestrial plants, but within the animal kingdom, they are reported only in few marine organism groups such as sponges (Kubanek et al. 2000), sea cucumbers (Yamanouchi 1955), and starfishes (Kitagawa and Kobayashi 1977). Echinoderms harbor in comparison to other marine invertebrates by far the most of the 350 reported saponin compounds.

Saponins are complex amphipathic glycosides composed of a steroid (largely found in sea stars) or triterpenoid aglycone (most commonly found in sea cucumbers) and a carbohydrate moiety (Minale et al. 1995). Saponins consist of hydrophilic (glycone) and hydrophobic (aglycone) components. The sugar moiety of saponins is mostly composed of glucose (Glc), xylose (Xyl), galactose (Gal), glucuronic acid (Glu), rhamnose (Rha), and/or methylpentose and is connected to the hydrophobic compartment (sapogenin) via glycosidic bonds. The nature of the side chains and the positions of various carbohydrate residues, or monosaccharide compositions, affect the membranotropic activities and functional properties of this chemical group.

Saponins show a broad range of bioactivities and ecological functions ranging from cytotoxic, hemolytic, antibacterial, antiviral, antifouling, antifungal, and anti-inflammatory activities, immunomodulatory effects, ichthyotoxicity, and deterrent/attractant properties for predators/symbionts (see Tables 7.2 and 7.3 for more details). Furthermore, the inter-

Table 7.3 Triterpene glycosides of different orders of holothurians and their bioactivity

Order	Family	Species	Saponin compounds	Biological activity	References
Apodida	Synaptidae	*Opheodesoma grisea*	n.d.	Hemolytic activity	Kalinin et al. (2008)
		Synapta maculata	Synaptoside A	Cytotoxic	Avilov et al. (2008)
			Synaptoside A_1	Antitumor	Avilov et al. (2008)
Elasipodida	Elpidiidae	*Kolga hyalina*	Kolgaosides A, B	Low cytotoxicity	Silchenko et al. (2014b)
		Rhipidothuria racovitzai	Achlioniceosides A_1–A_3	n.d.	Antonov et al. (2009)
Holothuriida	Holothuriidae	*Holothuria atra*	n.d.	Antifouling and antibacterial activities	Soliman et al. (2016)
			Holothurin A–B, Echinoside A–B	Antifungal	Kobayashi et al. 1991
			Ethanolic extracts	Antifungal and antibacterial	Abraham et al. (2002)
		Holothuria leucospilota	Holothurin A–B	Antimicrobial	Kitagawa et al. (1979, 1981d)
			Holothurin	Ichthyotoxic	Yamanouchi (1955)
			Leucospilotaside A–C, holothurin B, B_2	Leucospilotaside B: antitumor	Han et al. (2007b, 2008b, 2009a, 2010b)
			Holothurinoside E_1, holothurin A–B, B_3, desholothurin A, bivittoside D	Hemolytic activity	Van Dyck et al. (2010)
		n.d.	Holothurin A–B, A_2, holotoxin A_1	Immunomodulatory activity	Popov et al. (1994)
		Holothuria fuscocinerea	Holothurin	Hemolytic activity	Pocsidio (1983)
			Fuscocinerosides A–C, pervicoside C, holothurin A	Antifungal, cytotoxic	Zhang et al. 2006d
		Holothuria pulla	Holothurin	Hemolytic activity	Pocsidio (1983)
		Holothuria pervicax	Pervicosides A–C	Antifungal	Kitagawa et al. (1985, 1989)
		Holothuria mexicana	Holothurins A, B	Cytotoxic	Anisimov et al. (1980)
		Holothuria nobilis	Nobilisides A–D	Nobiliside A: antifungal, antitumor	Wu et al. (2006a, 2007a, 2009a), Zhang (2009), Guo and Xiong (2009) and Zhang and Zhu (2017)
			Echinoside A	Anticancer	Li et al. (2010)
		Holothuria scabra	24-dehydroechinoside A, echinoside A, holothurin A	Antifungal	Kobayashi et al. (1991)
			24-Dehydroechinoside A	Antitumor	Han et al. 2012
			Fusccosineroside C, echinoside A, holothurin A_1, A_4	Anticancer	Dang et al. (2007) and Han et al. (2012)
			Scabraside A,B, echinoside A, holothurin A_1	Antifungal	Han et al. (2008a, 2009b)
			Scabrasides A–D, fuscocineroside C	Antitumor	Han et al. (2009b, 2012)
			Holothurins A_3–A_4	Cytotoxic	Dang et al. (2007)
			Echinoside A and holothurin A_1–A_4	Cytotoxic	Han et al. (2009b)

(continued)

Table 7.3 (continued)

Order	Family	Species	Saponin compounds	Biological activity	References
			Crude extract	Antioxidant	Suwanmala et al. (2016)
			Ethanolic extracts	Antifungal and antibacterial	Abraham et al. (2002)
		Holothuria poli	Holothurins B_2–B_4, Holothurins A–B	n.d.	Silchenko et al. (2005c)
			methanol and aqueous extracts	Antifungal	Ismail et al. (2008)
			Bivittoside	Cytotoxic	Omran and Khedr (2015)
			Holothurinoside	Antifouling	Ozupek and Cavas (2017)
		Holothuria tubulosa	Holothurins A–B	n.d.	Silchenko et al. (2005c)
			Holothurinoside	Antifouling	Ozupek and Cavas (2017)
			Methanol and dichloromethane extracts	Anti-inflammatory	Herencia et al. (1998)
		**Holothuria fuscopunctata*	Impatienside B, arguside F, and pervicoside D	Antifungal	Yuan et al. (2009b)
			Axilogoside A, holothurin B	Antifungal	Yuan et al. (2008)
			Desulfated glycosides	Antifungal	Kobayashi et al. (1991)
		Holothuria forskali	Holothurinosides A–D	Antitumor, antiviral	Rodriguez et al. (1991)
		Holothuria floridana	n.d.	hypothermic, and hemolytic activities	Kaul (1986)
			Holothurins A_1–A_2, B_1	n.d.	Kuznetsova et al. (1982b), Oleinikova et al. (1982), and Oleinikova and Kuznetsova (1983)
			Holothurin A_1	Few inhibition of Na^+/K^+-ATPase activity	Gorshkova et al. (1989)
		Pearsonothuria graeffei	Disulfated Holothurin A	Hemolytic activity	Van Dyck et al. (2010)
			Desholothurin A, holothurinoside C	Hemolytic activity	Van Dyck et al. (2010)
			Holothurinoside J_1	Hemolytic activity	Van Dyck et al. (2010)
			Disulfated echinoside A	Stimulator of hepatic fatty acid β-oxidation and suppression of FA biosynthesis/anticancer	Zhao et al. (2011, 2012) and Wen et al. (2016)
			Disulfated echinoside A	Antimetastatic activity	Zhao et al. (2011)
			Echinoside A, disulfated echinoside A	Antitumor	Zhao et al. (2012)
			n.d.	Antihyperlipidemic activity	Hu et al. (2010)
		Holothuria grisea	Holothurin A_1	n.d.	Oleinikova et al. (1982)
			Griseaside A, 17-dehydroxyholothurinoside A	Cytotoxic	Yi et al. (2008)
		Holothuria edulis	Holothurin A	Anti-fungal	Kobayashi et al. (1991)
			Ethyl acetate fraction	Anti-inflammatory	Wijesinghe et al. (2015)
		Holothuria hilla	Hillasides A–C	Antitumor, cytotoxic	Wu et al. (2006b, 2007b, 2009b)
		Holothuria lessoni	Holothurinoside A_1, E_1	n.d.	Bahrami et al. (2014)
			Lessonioside A–D	Acetylated saponin	Bahrami et al. (2014) and Bahrami and Franco (2015)
			Lessonioside E–G, M	Nonacetylated saponin	Bahrami and Franco (2015)
			Holothurinoside X–Z	n.d.	Bahrami et al. (2014)

		Holothuria moebii	Sulfated and desulfated saponins	Cytotoxic	Yu et al. (2015)
		Holothuria sp.	n.d.	Antiviral	Farshadpour et al. (2014)
		Holothuria impatiens	Impatienside A[a], bivittoside D	Cytotoxic, Antitumor	Sun et al. (2007)
		Bohadschia argus	Bivittoside types	Antitumor	Kuznetsova et al. (1982a)
			Argusides A–E	Cytotoxic	Liu et al. (2007, 2008a, b)
			Holothurin C	Inhibition of Na^+/K^+-ATPase activity	Gorshkov et al. (1982)
		Bohadschia bivittata	Bivittosides A–D	Antifungal	Kitagawa et al. (1981c)
			Bivittosides A–B	Inhibition of Na^+/K^+-ATPase activity	Kitagawa et al. (1981c) and Gorshkova et al. (1989)
		Bohadschia vitiensis	Bivittoside D	Antiviral, anti-fungal, and spermicide	Lakshmi et al. (2008, 2012) and Maier (2008)
		Bohadschia marmorata	Impatiensides A[a]–B, marmortosides A–B, 25-acetoxybivittoside D, bivittoside D	Antifungal	Yuan et al. (2009a)
			Bivittosides	Antitumor	Kuznetsova et al. (1982a)
		Bohadschia cousteaui	Coustesides A–J	Antifungal	Elbandy et al. (2014)
		Bohadschia graeffei	Holothurin A, echinoside A	Antifungal	Kobayashi et al. (1991)
		Bohadschia subrubra	Impatienside A[a]; bivittoside C, D; araguside C; holothurinoside F, H, H_1, I, I_1, K_1	Hemolytic	Van Dyck et al. (2010)
		Actinopyga agassizi	Holothurin A	Ichthyotoxic	Chanley et al. (1959)
			24-Dehydroechinoside A	Ichthyotoxic	Kalinin et al. (2008)
			Holothurin	Antitumor	Sallivan et al. (1955)
			Holothurin	Antiparasitic (against *Trypanosoma lewisi*)	Styles (1970)
			Holothurin	Mitogenic activity	Nigrelli and Jakowska (1960)
			n.d.	Antibacterial, immunomodulatory effect	Kalinin et al. (2008)
		Actinopyga lecanora	n.d.	Hemolytic activity	Poscidio (1983)
			Holothurins A–B	Antifungal	Kumar et al. (2007)
			Holothurins A, A_1, B, lecanorosides A and B	Antitumor	Zhang et al. (2008)
			Holothurin A, holothurin B	Antiparasitic	Singh et al. (2008)
			n.d.	Antibacterial	Ghanbari et al. (2012)
		Actinopyga echinites	Echinosides A–B	Antifungal, antischistosomal	Kitagawa et al. (1980) and Melek et al. (2012)
			Ethanolic extracts	Antifungal and antibacterial	Abraham et al. (2002)

(continued)

Table 7.3 (continued)

Order	Family	Species	Saponin compounds	Biological activity	References
		Actinopyga mauritiana	Echinosides A–B, 24- ehydroechinosides A–B	Antifungal	Kobayashi et al. (1991)
			n.d.	Antineoplastic and cytotoxic	Pettit et al. (1976)
		Actinopyga flammea	Echinosides, Holothurinogenins	Antitumor, antifungal	Bhatnagar et al. (1985) and Mondol et al. (2017)
		Actinopyga miliaris	Ethanolic extracts	Antifungal and antibacterial	Abraham et al. (2002)
Dendrochirotida	Cucumariidae	*Cucumaria japonica*	Cucumarioside	Immunomodulatory effect	Polikarpova et al. (1990)
			Cucumarioside	Antifungal	Batrakov et al. (1980)
			Cucumarioside	mitogenic Antiproliferative activity	Turischev et al. (1991)
			Cucumarioside $A_{4\text{-}2}$	Hemolytic activity, immunomodulatory effect, antiviral	Aminin et al. (2001) and Kalinin et al. (2008)
			Cucumarioside A_2–2	Hemolytic, cytotoxic, inhibition of Na/K+-ATPase activity, immunomodulatory effect, antiviral, antitumor	Avilov et al. (1991b), Kalinin et al. (1996), Aminin et al. (2001), Agafonova et al. (2003), Menchinskaya et al. (2014), and Pislyagin et al. (2017)
			Cucumariosides $A_{1\text{-}2}$, $A_{2\text{-}3}$, $A_{2\text{-}4}$, $A_{4\text{-}2}$	n.d.	Avilov et al. (1991b)
			Cucumarioside A_3	Hemolytic, immunomodulatory effect	Aminin et al. (2001)
			Cucumariosides $A_{7\text{-}1}$, $A_{7\text{-}2}$, $A_{7\text{-}3}$	Hemolytic, cytotoxic, immunomodulatory effect	Drozdova et al. (1993), Kalinin et al. (1996), Aminin et al. (2001), and Agafonova et al. (2003)
			Cucumarioside A_6–2	Antitumor, cytotoxic, hemolytic, immunomodulatory effect	Kalinin et al. (1996), Drozdova et al. (1997), and Aminin et al. (2001)
			Cucumariosides $A_{0\text{-}1}$, $A_{0\text{-}2}$, $A_{0\text{-}3}$	n.d.	Drozdova et al. (1993)
			Cucumarioside A_3	Antitumor, hemolytic	Kalinin et al. (1996) and Drozdova et al. (1997)
			Cucumarioside G_1	Inhibition of Na/K+-ATPase activity	Anisimov et al. (1983)
			Cumaside	Immunomodulatory and hemolytic effect	Aminin et al. (2006)
			Cucumarioside	Immunomodulatory effect, antibacterial, Antiviral	Sedov et al. (1984, 1990), Grishin et al. (1990), and Aminin (2016)
		Cucumaria frondosa	Frondoside A	Antiproliferative effects, Antitumor, anticancer, Immunomodulatory effect	Al Shemaili et al. (2014), Girard et al. (1990), Al Marzouqi et al. (2011), Attoub et al. (2013), Ma et al. (2012), and Aminin et al. (2008)
			Frondoside D	n.d.	Yayli and Findlay (1999)
			Frondoside C	Antitumor	Avilov et al. (1998)
			Frondosides B, $A_{2\text{-}1}$–$A_{2\text{-}8}$	n.d.	Findlay et al. (1992) and Silchenko et al. (2005a, b)
			Frondoside $A_{7\text{-}2}$, $A_{7\text{-}3}$, $A_{7\text{-}4}$, isofrondoside C	n.d.	Silchenko et al. (2007a)

		**Cucumaria echinata*	Cucumechinosides A–F	Antifungal, anticancer, antiprotozoal	Miyamoto et al. (1990b)
			Cucumechinol A–C	n.d.	Miyamoto et al. (1990a)
			Disulfated Penaustrosides A–B	n.d.	Miyamoto et al. (1992)
			CEL-I	Hemolytic activity	Hatakeyama et al. (1999)
			CEL-III	Hemolytic activity	Oda et al. (1999)
		Cucumaria fallax	Fallaxosides B_1, C_1– C_2, D_1–D_7	Cytotoxic, hemolytic	Silchenko et al. (2016a)
		Cucumaria okhotensis	Okhotosides B_1–B_3	Antitumor, cytotoxic	Silchenko et al. (2008)
			Okhotosides $A_{2\text{-}1}$, $A_{1\text{-}1}$, B_1–B_3	Immunomodulatory activity, cytotoxic	Silchenko et al. (2007b, 2008) and Aminin et al. (2010)
			Frondosa A_1	Immunomodulatory activity	Aminin et al. (2010)
		Cucumaria Conicospermium	Cucumarioside $A_{2\text{-}5}$, $A_{3\text{-}2}$, $A_{3\text{-}3}$, Isokoreoside A, koreoside A	n.d.	Avilov et al. (2003)
		Cucumaria lefevrei	Lefevreosides A_1, A_2, C,D	n.d.	Rodriguez and Riguera (1989)
		Cucumaria koreaensis	Koreoside A	n.d.	Avilov et al. (1997)
		Cucumaria miniata	Cucumarioside $A_{7\text{-}3}$	n.d.	Drozdova et al. (1997)
		Mensamaria intercedens	Intercedensides A–C, D–I	Antitumor, cytotoxic	Zou et al. (2003, 2005)
		Hemioedema spectabilis	Hemoiedemosides A–B	Cytotoxic, antifungal	Chludil et al. (2002a)
		**Pentacta quadrangularis*	Phylinopside E (PE)	Antitumor, Antiangiogenesis, cytotoxic	Tian et al. (2005, 2007)
			Phylinopsides A,B, E, F	Cytotoxic	Yi et al. (2006) and Zhang et al. (2006a)
			Phylinopsides A–B, pentactaside I, II, and III	Cytotoxic	Han et al. (2010a)
			Pentactaside B, C	Antitumor	Han et al. (2010c)
		Pentacta australis	Desulfated penaustrosides A–D	n.d.	Miyamoto et al. (1992)
		Actinocucumis typica	Typicosides A_1, A_2, B_1	Immunomodulatory effect, cytotoxic	Pislyagin et al. (2014)
			Typicosides A_1, A_2, B_1, C_1, C_2, intercedenside A, holothurin B_3	Antifungal, cytotoxic	Silchenko et al. (2013b)
		Colochirus robustus	Colochiroside E	n.d.	Silchenko et al. (2016c)
			Colochirosides D, A_1–A_3, B_1–B_3	Cytotoxic, hemolytic activity	Silchenko et al. (2015a, 2016c, b)
		***Cercodemas anceps*	Colochiroside A	Antitumor	Cuong et al. (2015)
			Cercodemasoides A–E	Cytotoxic	Cuong et al. (2015)
		**Pseudocnus dubiosus leoninus*	Pseudocnoside A	Anticancer, antiproliferative	Careaga et al. (2014)

(continued)

Table 7.3 (continued)

Order	Family	Species	Saponin compounds	Biological activity	References
		Staurocucumis liouvillei	Liouvillosides A–B	Cytotoxic, antiviral	Maier et al. (2001)
			Liouvillosides A_1–A_5, B, B_2	n.d.	Antonov et al. (2008, 2011)
		**Staurocucumis turqueti*	Turquetoside A	n.d.	Silchenko et al. (2013d)
		Pseudocolochirus violaceus	Violaceusides A, B, C, E, I–III	Cytotoxic	Zhang et al. (2006b, c) and Silchenko et al. (2014a)
			Violaceuside D, G	Cytotoxic	Silchenko et al. (2014a)
		**Duasmodactyla kurilensis*	Kurilosides A, C	n.d.	Avilov et al. (1991a)
	Sclerodactylidae	*Eupentacta fraudatrix*	Cucumarioside G_1	Cytotoxic, hemolytic, inhibition of Na/K+-ATPase activity	Gorshkov et al. (1982), Afiyatullov et al. (1985), and Kalinin et al. (2008)
			Cucumarioside G_2	Hemolytic activity	Avilov et al. (1994)
			Cucumariosides H_1–H_8	Hemolytic activity, cytotoxic	Silchenko et al. (2012c)
			Cucumarioside C	Cytotoxic	Anisimov et al. (1974)
			Cucumariosides A_1–A_{10}, A_{14}, A_{15}, A_8	Antifungal, hemolytic activity	Melek et al. (2012) and Silchenko et al. (2012a, b)
			Cucumarioside B_2	Antifungal	Melek et al. (2012) and Silchenko et al. (2012a, b, d)
			Cucumariosides G_1, G_2, G_4, $G_{4\text{-}A}$	Hemolytic activity	Kalinin et al. (1992a, b, 2008)
			Cucumariosides F_1, F_2	n.d.	Popov et al. (2014)
			Cucumariosides I_1–I_3	Cytotoxic and immunostimulatory activities	Silchenko et al. (2013a, b, c)
			Cucumarioside B_1	Hemolytic activities, antifungal	Melek et al. (2012) and Silchenko et al. (2012a, b, d)
			Cucumariosides A_1–A_{15}	Cytotoxic	Silchenko et al. (2012a)
		**Cucumaria fraudatrix*	Cucumariosides G_1, G_3, $G_{3\text{-}A}$	Cytotoxic, hemolytic activity	Afiyatullov et al. (1985) and Popov (2002)
		Cladolabes schmeltzii	Cladolosides A_1–A_6, B $_1$–B_2, C, C_1–C_4, D, D_2, E_1, E_2, F_1, F_2, G, H_1, H_2, J_1, K_1, K_2, L_1, M, M_1, M_2, N, I_2, O, P, P_1, P_3, Q, R	Cytotoxic	Silchenko et al. (2013e, 2014c, 2015b, 2017a, 2018a, b)
	Psolidae	*Psolus fabricii*	Psolusoside A	Hemolytic activity	Kalinin et al. (1996)
			Psolusosides A, B	Inhibition of Na^+/K^+-ATPase activity	Kalinin et al. (1989a) and Gorshkova et al. (1999)
		Psolus eximius	Eximisoside A	n.d.	Kalinin et al. (1997)
		Psolus patagonicus	Patagonicosides A–C	Antifungal, cytotoxic	Murray et al. (2001), Muniain et al. (2008) and Careaga et al. (2011)
	Phyllophoridae	*Pentamera calcigera*	Calcigerosides B, C_1, C_2	Cytotoxic	Avilov et al. (2000b)
			Cucumarioside G_2	No cytotoxicity	Avilov et al. (2000b)
			Calcigerosides D_1–D_2, E	n.d.	Avilov et al. (2000a)
		Neothyonidium magnum	Magnumosides A_1–A_4, B_1–B_4, C_1–C_4	Cytotoxic, hemolytic	Silchenko et al. (2017b)

Synallactida	Stichopodidae	****Apostichopus japonicus**	Holotoxin A, B, C	Antifungal	Kitagawa et al. (1976) and Maltsev et al. (1984, 1985)
			Holotoxin A_1	Antiprotozoal, antitumor	Kitagawa et al. (1976) and Anisimov et al. (1983)
			Holotoxin A_1, cladoloside	Neurotoxic, cytotoxic	Yun et al. (2018)
			Holotoxin A_1	Cytotoxic, antiproliferative activity	Ishida et al. 1993 and Popov et al. 1994
			Holotoxins A_1, B_1	Inhibition of Na^+/K^+-ATPase activity	Maltsev et al. (1984) and Gorshkova et al. (1989)
			Apostichoposide C	Inhibition of Na^+/K^+-ATPase activity	Gorshkova et al. (1989)
			Holotoxin A_1, B_1 and holothurin A	Contraceptive effect	Mats et al. (1990)
			Cladoloside B	Antifungal	Wang et al. (2012)
			Holotoxins A_1, B_1, D_1, A	Antifungal	Wang et al. (2012)
			25,26-Dihydroxy-holotoxin A_1	Antifungal	Wang et al. (2012)
			Holotoxins D–G	Antifungal	Wang et al. (2012)
			(Nortriterpene glycoside) 26-nor-25-oxo-holotoxin A_1	Antifungal	Wang et al. (2012)
			Holotoxins F, G, H	Antifungal	Liu et al. (2012) and Wang et al. (2012)
		**Stichopus japonicus*	Stichopogenin A_4, A_2 (genuine aglycone holotoxin A)	Antifungal	Kitagawa et al. (1976)
			Crude saponin	Antioxidant	Husni et al. (2009)
		Stichopus chloronotus	Chloronoside A, C, D, E	Antimicrobial, antifungal, cytotoxic, antitumor	Anisimov et al. (1983) and Maltsev et al. (1985)
			Stichoposides C, D, E	Inhibition of Na/K+-ATPase activity	Gorshkova et al. (1989)
			Stichlorosides A_1–A_2, B_1, B_2, C_1, C_2	Antifungal	Kitagawa et al. (1981a, b)
			Stichoposides A, B	n.d.	Sharypov et al. (1981)
			n.d.	Antineoplastic and cytotoxic	Pettit et al. (1976)
		Stichopus horrens	Stichorrenosides A–D, stichoposide A	Cytotoxic	Cuong et al. (2017)
			Stichorrenosides E	Cytotoxic	Vien et al. (2018)
		**Stichopus variegatus*	Variegatusides A–F, holothurin B	Antifungal	Wang et al. (2014)
		Stichopus hermanni	Stichlorosides A_1, A_2, B_1, B_2, C_1, C_2	Antifungal	Kobayashi et al. (1991)
		**Stichopus parvimensis*	Parvimosides A, B	n.d.	De Moncerrat Iñiguez-Martinez et al. (2005)
		**Stichopus multifidus*	Astichoposide C	Inhibition of Na\K+-ATPase activity	Gorshkov et al. (1982)
		Thelenota ananas	Thelenotosides A–B	Antifungal	Stonik et al. (1982) and Maltsev et al. (1985)
			Saponin compounds	Antitumor	Pettit et al. (1976)
			Thelenotoside A	Immunomodulatory effect	Gorshkova et al. (1989)
			Stichlorosides A_1, A_2, B_1, B_2, C_1, C_2	Antifungal	Kobayashi et al. (1991)

(continued)

Table 7.3 (continued)

Order	Family	Species	Saponin compounds	Biological activity	References
			Telothurins A–B	Antitumor	Kuznetsova et al. (1982a)
			n.d.	Antineoplastic and cytotoxic	Pettit et al. (1976)
			n.d.	Antiviral	Hegde et al. (2002)
		Thelenota anax	Stichlorosides A_1, B_1, C_1	Antifungal	Kobayashi et al. (1991)
			Telothurin	Antitumor	Kuznetsova et al. (1982a)
			Stichoposides C–D	Antitumor, anticancer	Yun et al. (2012) and Park et al. (2014)
		Australostichopus mollis	Neothyonidioside	Antifungal	Yibmantasiri et al. (2012)
			Mollisosides A, B_1– B_2	n.d.	Moraes et al. (2005)
	Synallactida	*Synallactes nozawai*	Synallactosides A_1, A_2, B_1, B_2, C	n.d.	Silchenko et al. (2002)
Persiculida	Pseudostichopodidae	*Pseudostichopus trachus*	Pseudostichoposides A,B	n.d.	Kalinin et al. (1989b) and Silchenko et al. (2004)

[a]Marmoratoside A = impatienside A (Van Dyck et al. 2010)

*Based on WoRMS (2019), the accepted names changed from: *Stichopus multifidus* to *Astichopus multifidus; Neothyonidium magnum* to *Massinium magnum; Pseudocnus dubiosus leoninus* to *Pentactella leonina; Cucumaria fraudatrix* to *Eupentacta fraudatrix; Holothuria axiologa* to *Holothuria fuscopunctata; Penctata quadrangularis* to *Cholochirus quadrangularis; Stichopus variegatus* to *Stichopus horrens; Stichopus parvimensis* to *Apostichopus parvimensi; Duasmodactyla kurilensis* to *Thyonidium kurilensis; Pentacta quadrangularis* to *Colochirus quadrangularis; Bohadschia bivittata* to *Bohadschia vitiensis; Cucumaria echinata* to *Pseudocnus echinatus; Stichopus japonicus* to *Apostichopus japonicus*

**Synonymised names: *Staurocucumis turqueti* = *Cucumaria turqueti/Cucumaria spatha; Cercodemas anceps* = *Colochirus anceps*

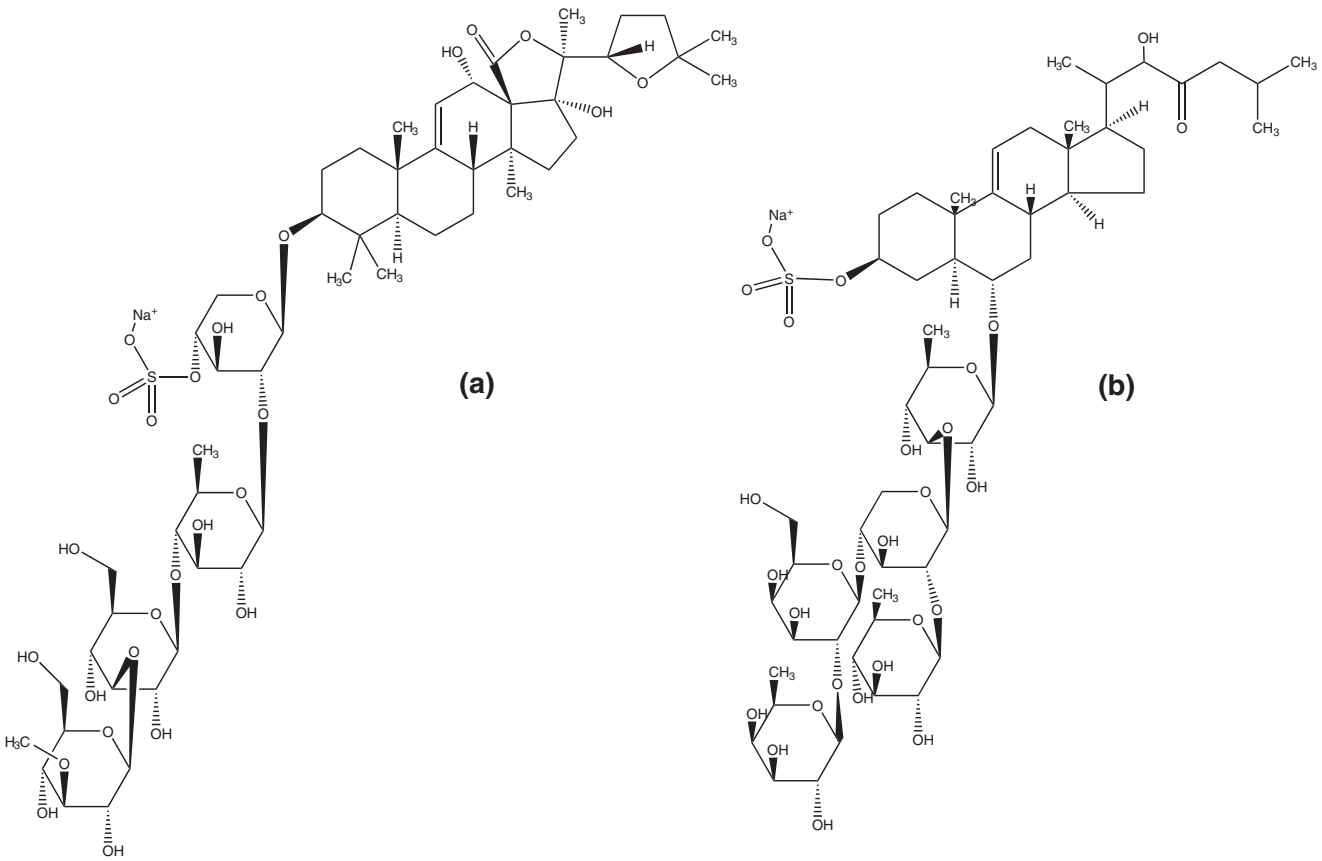

Fig. 7.4 Examples of (**a**) a triterpene glycoside structure: Holothurin A isolated from the sea cucumber *Holothuria leucospilota* (Kitagawa et al. 1981d) and (**b**) a steroidal glycoside structure: Thornasteroside A isolated from the sea star *Acanthaster planci* (Kitagawa and Kobayashi 1978) (produced with ChemDraw, version 16.0.1.4 (77))

actions between aglycone components (i.e., sapogenin) and sterols of the cell membranes can result in a saponification process that may lead to cell lysis (Bahrami et al. 2016).

The sulfate group seems to be one of the most essential groups in most saponins derived from ophiuroids, asteroids (Table 7.2), and holothuroids (Table 7.3). However, there is a basic difference in the position of this functional group between echinoderms (Fig. 7.4). For both sea stars and brittle stars, the sulfate group is located in the hydrophobic part (aglycone) of the molecule, whereas in holothurians the sulfate group is placed within the hydrophilic moiety (glycone) (Kornprobst et al. 1998). The structural differences of asterosaponin and triterpene glycosides showed that not only the presence but also the position of the sulfate groups may be important, resulting in potentially different biological activities of saponins (Maier 2008; Malyarenko et al. 2015).

As the sea cucumbers contain the highest variety of saponin species, we will next (see Sect. 7.3.1) focus on the distribution and function of triterpene glycosides that have been reported exclusively from holothurians.

7.3.1 Structural Diversity of Saponins in Holothuroids

The first report of polar and low volatile triterpene glycosides within the animal kingdom was in 1952 and originated from a sea cucumber extract (Nigrelli and Zahl 1952).The initial studies on the bioactive properties of compounds derived from sea cucumbers explained the ichthyotoxic activities of saponins, which were extracted from the body wall and the CTs of *Holothuria leucospilota* and *Actinopyga agassizi* (Nigrelli and Jakowska 1960; Yamanouchi, 1955). Most of the subsequently identified saponins were mainly isolated from three families of sea cucumbers: Holothuriidae, Stichopodiidae, and Cucumariidae (see Table 7.3).

The chemical structure of saponins in holothurians can be very complex in terms of the presence/absence and position of different functional groups (e.g., hydroxyl groups), which may differentiate them from other echinoderms as well as from each other marine invertebrates (Bahrami et al. 2014). The generic name of holothurian-derived saponins is Holothurin, which are nearly all 3β-glycosylated saponins

(Kornprobst et al. 1998). In most sea cucumbers, triterpene glycosides contain the aglycone lanosterol with an 18(20)-lactone (e.g., holostane 3β-ol; Kalinin 2000; Caulier et al. 2011) and an oligosaccharide chain that consists of D-Xyl, D-Quinov, D-Glc, D-3-O-methyl-Glc, and D-3-O-methyl-Xyl (Caulier et al. 2011; Bahrami et al. 2016).

Triterpene glycosides exhibit different bioactivities, which might aid the likelihood of survival for its producing organisms. This is also highlighted by their broad bioactivities as well as their broad ecological functions (e.g., antipredatory defense). Although the structure of each unit affects the bioactivity of the compound, linear oligosaccharide structures (i.e., tetraosides) have shown to be the optimum quantity of monosaccharide units in the glycoside (Minale et al. 1995; Kalinin et al. 2008). Furthermore, allelopathic properties of saponins, as well as the presence of various functional groups like amides, hydroxyl groups, acetyl groups, and sulfate groups in different species of sea cucumber, can inhibit larval attachment of macroorganisms and also affect the growth of different strains of gram-positive and gram-negative bacteria (Soliman et al. 2016). By changing the hydrophobic-hydrophilic balance of bacterial cells, extracted saponins may affect permeability and stability of the bacterial cell wall, which in turn can ultimately lead to cellular death (Lawrence et al., 1957; Soliman et al. 2016). Additionally, due to their hydrophilic properties, saponins regulate oocyte maturation and can thus affect the reproduction cycle of organism by synchronizing the maturation process (Kalinin et al. 2008).

The vast chemical diversity of saponin in sea cucumbers makes them effective models for studying their biochemical evolution and applying these compounds as potential holothurian chemotaxonomic markers (Kalinin et al. 1996, 2008; Kalinin 2000). Depending on the taxonomic group of sea cucumbers, the number, composition, and location of monosaccharide units, and position of functional groups in the holostane skeleton (i.e., hydroxyl, acetylate, sulfate, double bonds, etc.) may affect the bioactivity of the compounds (Stonik 1986; Kalinin 2000). For example, the presence of trisulfated glycosides in members of the family Cucumariidae is unique for this taxonomic group (Bahrami et al. 2016). Recent chemotaxonomic analysis supported the evolution of saponins in both glycone and aglycone moieties.

The general trend of glycone evolution in Holothuroidea is from non-sulfated to sulfated compounds. Bondoc et al. (2013) studied saponins from three species of Holothuroidea by using MALDI[2]-FTICR[3] MS[4] and nano-HPLC[5]-chip Q-TOF[6]-MS, and by applying maximum likelihood analysis, molecular biology, and evolutionary software packages, they created mass chemical and genetic fingerprints of saponins. They concluded that evolution of saponins leads to glycone parts with higher membranolytic activities and hydrophilicity with lower metabolic cost (Kalinin and Stonik 1996; Bondoc et al. 2013; Kalinin et al. 2015). Therefore, the glycone evolution of Holothuroidea was likely in the following order (Kalinin et al. 2016):

1. Transition from non-sulfated to sulfated hexaoside or pentaosides
2. Changing from hexaoside and pentaosides to linear tetraosides and biosides:
   (a) Carbohydrate contains sulfate group at C-4 of first xylose unit.
   (b) Shifting sugars with C-6 Glc and 3-O-methyl-Glc to sulfated at C-4 of first xylose

Kalinin et al. (2015) mentioned that sulfated tetraosides are a common characteristic of Holothuria and Actinopyga; however, sea cucumbers of the genus *Bohadschia* contain both non-sulfated and sulfated carbohydrate units (i.e., hexaosides and tetraosides). Bivittoside D extracted from *Bohadschia vitiensis* is a hexaoside non-sulfated glycoside that evolved to a sulfated tetraoside (Holothurin A_2), which has been also found in *Holothuria scabra* (Dang et al. 2007) and *Pearsonothuria graeffei* (Zhao et al. 2011). Further structural modification leads to compounds with two monosaccharides (i.e., biosides such as echinoside B) from *Holothuria leucospilota* (Han et al. 2009a) and *Actinopyga echinites* (Kitagawa et al. 1985). The general direction of aglycone evolution is more complicated and depends on the presence or absence of lactone, keto, hydroxyl groups, as well as position of double bonds (Kalinin et al. 2015):

1. Presence/absence of lactone: It shifts from lanostane derivatives without lactone to lanostane with an 18(16)-lactone and holostane with an 18(20)-lactone.
2. Shifting the position of double bonds and the keto group. In general, transition of aglycones occurs from low oxidation to higher oxidized compounds.
   (a) Transition of aglycone compounds having a 7(8) double bond, and a carbonyl group at C-16, to compounds oxidized at C-22 or C-23 without the oxygen at C-16
   (b) Transition of aglycone molecule from 9(11) double bond and C-16 keto group to compounds having oxygen at C-16, and then to compounds without oxygen, but containing a 12α-hydroxyl group

[2]Matrix-assisted laser desorption/ionization.

[3]Fourier transformation cyclotron resonance.

[4]Mass spectrometry.

[5]Nano-high-performance liquid chromatography.

[6]Quadrupole time-of-flight.

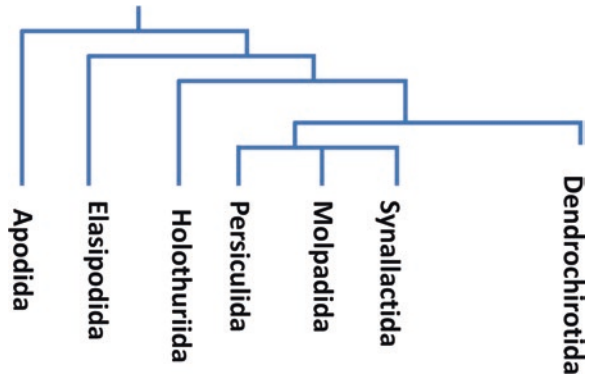

Fig. 7.5 Phylogeny of Holothuroids. Produced based on Miller et al. (2017). Holothuriida is the new accepted name for the order of Aspidochirotida

Overall, based on morphological, molecular, and paleontological analysis, there has been a clear evolutionary distance between Apodida and other species of the orders Dendrochirotida and Holothuriida (Fig. 7.5; Avilov et al. 2008). Several studies reported that the presence of the 3-O-methyl group in the terminal monosaccharide units of holothurians (*Psolus fabricii*, *Cucumaria japonica*, *Hemoidema spectabilis*, etc.) increased the membranolytic activities of the compound. Kalinin et al. (2008) described that during evolution of the terminal monosaccharide unit from glucoronic acid (GlcA) to Glc, the 3-O-methyl group was conserved due to the protective properties against predatory fish.

A unique group of sea cucumbers are the Synallactida. They are mostly epibenthic and their remarkable defense behavior is shedding (Kropp 1982). Their typical chemical defenses are holotoxins, stichoposides, and stichlorosides (Table 7.3). The common characteristics of stichoposides and holotoxins are the presence of a double bond at C-25 (C-26), while the presence of α-acetoxy group at C-23 and a 3-O-methyl-D-Glc in their polysaccharide chain are another feature of stichoposides. The presence of a keto-group at C-16 is observed for most holotoxins. Interestingly, there is a sulfate group present in stichoposides (Mondol et al. 2017). Thus, the presence of a particular aglycone or glycone glycoside can be a taxonomic marker for certain genera such as the genera *Bohadschia, Pearsonothuria*, and *Actinopyga* (Kalinin et al. 2016). The presence, expellability, and stickiness of CTs of Holothuriidae (i.e., *Bohadschia argus*, *Holothuria forskali*) affect the chemical diversity of triterpene glycosides of the sea cucumbers (Honey-Escandón et al. 2015). Among Holothuriidae, the genus *Bohadschia* is considered a more primitive group since it contains well-developed CTs with expellability and stickiness and possesses non-sulfated and less-oxidized glycosides in both the CT and body wall (Kalinin et al. 1996, 2008; Honey-Escandón et al. 2015). In contrast, more sulfated and oxidized glycosides have been reported within species without CTs or with dysfunctional CTs such as *Holothuria hilla* and *Actinopyga echinites* (Honey-Escandón et al., 2015). However, members of Dendrochirotida and Apodida also showed different patterns. Species of the order Apodida such as *Synapta maculata* are considered the most primitive group of Holothurians. They contain 3-O-methyl Glc-A in a carbohydrate chain and an 8(9) double bond in the aglycone moiety, which affects their membranolytic activity and hydrophilicity of the glycosides (Avilov et al. 2008).

7.4 Discussion and Conclusions

Predation, the biological interaction where a predator eats its prey, is a main driving force for community structure and ecosystem organization (Duffy and Hay 2001). It has been suggested that before the development of physical defenses, echinoderms used initially maternally derived chemical defenses from early larval stages to protect themselves against predators (Iyengar and Harvell 2001). Therefore, secondary metabolites play an important role in chemical defense of marine sessile and slow moving organisms and thus may affect and shape the community structure and increase the level of biodiversity of the ecosystem (Paul et al. 2007). Unfortunately, there is still a lack of information with regard to the ecological function of many MNPs, especially from echinoderms, while various pharmacological activities (e.g., antiviral, antitumor) have been widely reported. This represents a research opportunity for chemical ecologists who want to investigate how small modifications in molecules can affect ecological functions and community structure.

As summarized in Table 7.2, echinoderms have proven to be a rich source of bioactive compounds with most reported compounds in Asteroids and Holothuroids reported as saponins. Although various steroidal compounds of starfishes have been reported, only a few studies have investigated the biological activities of these compounds. Within ophiuroids, steroidal compounds, terpenes, and carotenoids have been isolated, and their mode of action has been summarized as antiviral and antitumor activities (Table 7.2).

The class Holothuria is a particularly rich source of MNPs with a multitude of reported activities. In the past decades, sea cucumbers have been increasingly harvested and consumed due to their nutritional values (high protein, low sugar, and no cholesterol (Liu et al. 2007, 2002; Wen et al. 2010) and their use in traditional medicine. Although a wide spectrum of bioactivities such as cytotoxic, hemolytic, antifungal, and immunomodulatory properties have been described for different sea cucumbers, in the extraction and compound purification process, often compounds with different chemical structures were combined, and thus the bio-

logical function of the individual compounds remain largely unknown. Therefore, their pharmaceutical potential has not yet been fully explored, which make them still promising candidates for the discovery of future MNPs with novel pharmaceutical applications. Furthermore, past studies focused largely on shallow-water holothurians, whereas deep-water specimens encounter particular harsh physicochemical conditions. Such conditions include strong hydrostatic pressure, low temperature, and possibly oxygen shortage, which could affect formation, structure, gene regulation, and biosynthesis of secondary metabolites, thus making deep-water specimens a potential interesting target for future MNP screening campaigns.

Saponins are highly diverse, common, and abundant MNPs in echinoderms. Among this group of the secondary metabolites, holothurins, holotoxins, cucumariosides, and echinosids are the most abundant compounds in various genera of sea cucumbers (Table 7.3). Most of the reported triterpene glycosides in sea cucumbers showed cytotoxicity as well as antifouling, antifungal, and antibacterial effects of saponins (Miyamoto et al. 1990b; Aminin et al. 2015; Soliman et al. 2016), providing sea cucumbers with an effective chemical defense mechanism against microbial attacks, fouling organisms, and potentially predators.

The principal mechanisms for the bioactivities of triterpene glycosides are most likely changing membranolytic effects and increased hydrophilicity of the compounds, which may not only affect their bioactivities but also make them potential trophic and taxonomic markers. Depending on the marine habitat and the defensive responses of holothurians, each group contains their own special mixture of saponins, which are often unique chemical signatures and thus can be used in chemotaxonomy to differentiate most holothurians at the family level. Furthermore, by studying structure-activity relationships (SAR), taxonomists may be able to predict physiological differences and their ecological role within the organisms.

Defense responses of holothurians vary at order or family levels, which is to some extend reflected in the stereochemistry of the saponins. The general evolution of aglycone is based on the presence/absence or position of lactone, keto, hydroxyl groups, and double bonds, which leads from low oxidized to more oxidized compounds. The direction of glycone evolution depends on the presence/absence or number and position of sulfate and acetoxy groups, type of sugar units and their (non)linear structure, as well as position of methyl group. For example, Apodida are considered as the most primitive sea cucumbers due to the presence of 3-O-methyl Glc-A in the glycone and 8(9) double bond in the aglycone moiety. Among Holothuriida, *Bohadschia* is the most primitive genus due to the presence of non-sulfated glycosides and functional CT.

In summary, studying the evolutionary pattern of structure-function relationships of holothurian's triterpene glycosides helps to understand their chemical-structural diversity, taxonomic distribution, ecological function, as well as bioactivity of the molecules, which can lead to a more targeted and efficient assessment of MNPs with novel pharmacological activities.

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Appendix

This article is related to the YOUMARES 9 conference session no. 9: "Biodiversity of Benthic Holobionts: Chemical Ecology and Natural Products Chemistry in the Spotlight." The original Call for Abstracts and the abstracts of the presentations within this session can be found in the Appendix "Conference Sessions and Abstracts", Chapter "7 Biodiversity of Benthic Holobionts: Chemical Ecology and Natural Products Chemistry in the Spotlight", of this book.

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