# 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

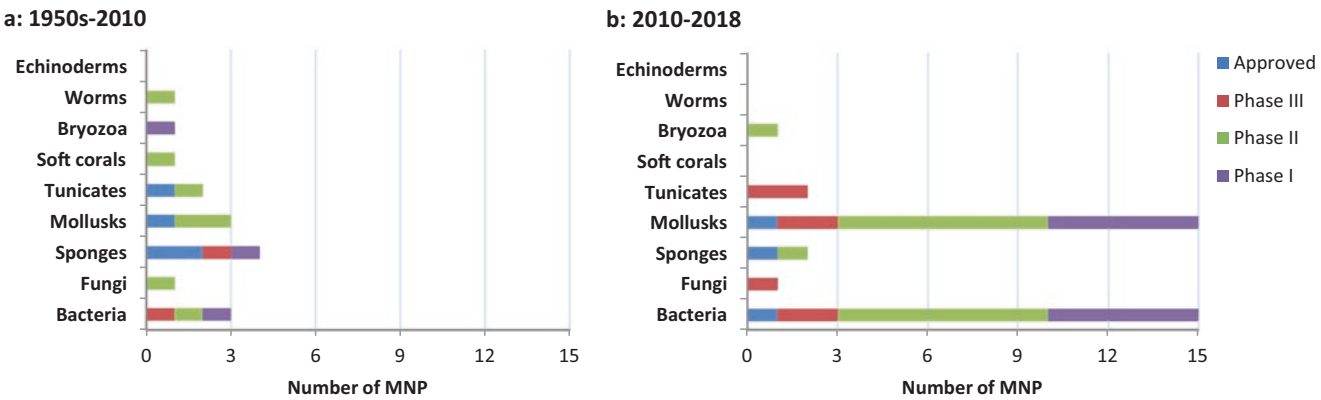


**Fig. 7.1** Overview of marine organisms from which MNPs entered the pharmaceutical pipeline (**a**) from 1950s to 2010 and (**b**) from 2010 to 2018. (Compiled with data from Mayer and Hamann 2002; Mayer et al. 2017; http://marinepharmacology.midwestern.edu)

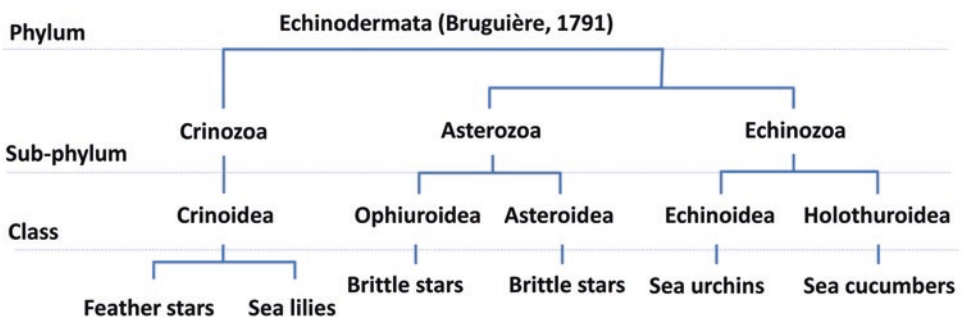


**Fig. 7.2** Phylogenetic tree for the phylum Echinodermata (modified after Telford et al. 2014)

**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

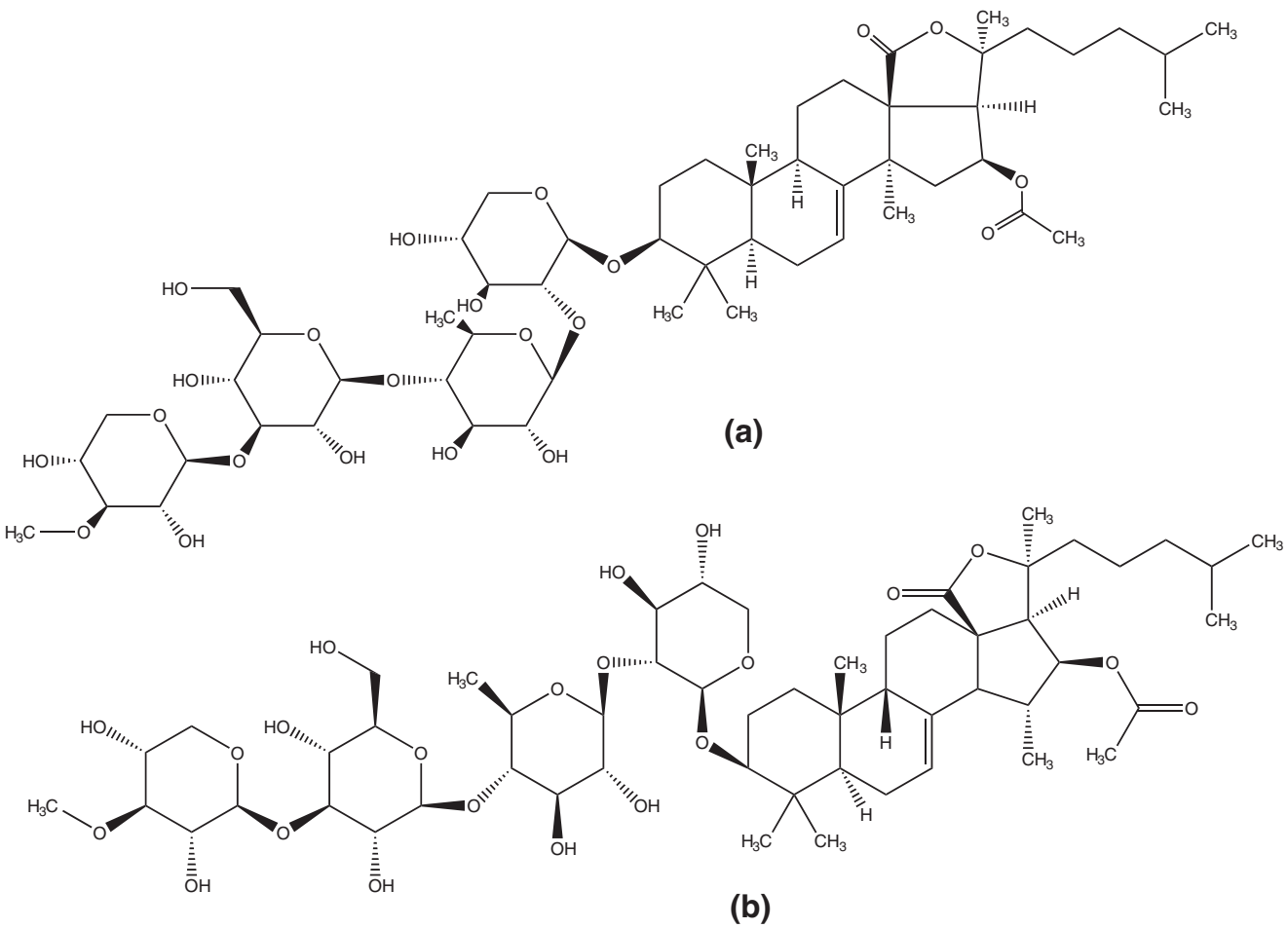


**Fig. 7.3** (**a**) Rollentoside B isolated from *Asterias rollestoni* and (**b**) Cucumarioside $A_{15}$ isolated from *Eupentacta fraudatrix* with similar chemical formula of $C_{55}H_{88}O_{22}$ (produced with ChemDraw, version 16.0.1.4 (77))

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*

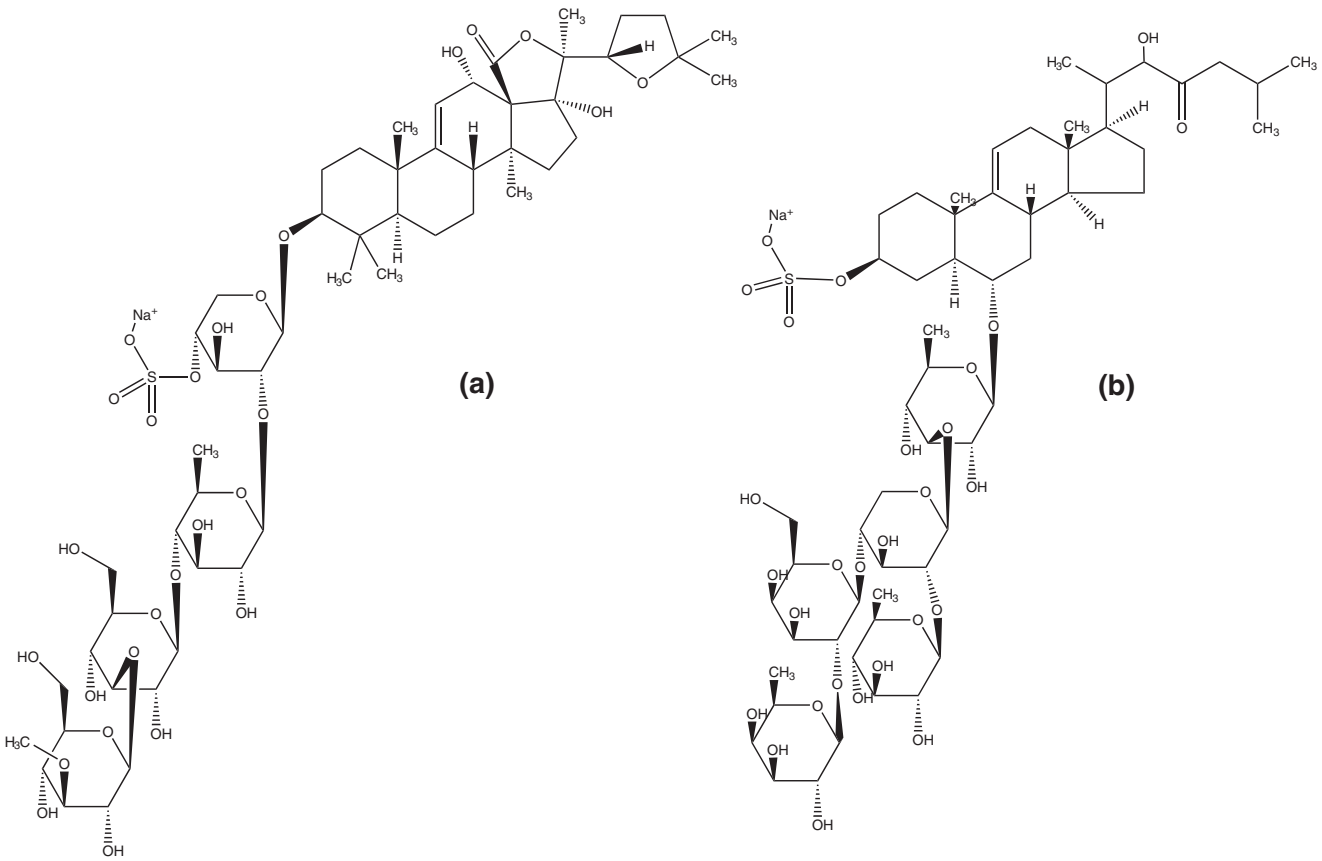


**Fig. 7.4** Examples of (**a**) a triterpene glycoside structure: Holothurin A isolated from the sea cucumber *Holothuria leucospilota* (Kitagawa et al. 1981d) and (**b**) a steroidal glycoside structure: Thornasteroside A isolated from the sea star *Acanthaster planci* (Kitagawa and Kobayashi 1978)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

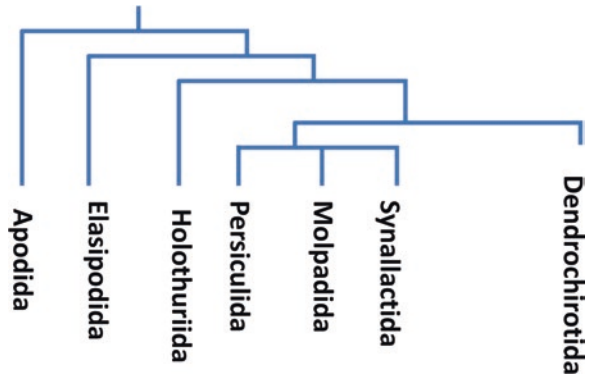


**Fig. 7.5** Phylogeny of Holothuroids. Produced based on Miller et al. (2017). Holothuriida is the new accepted name for the order of Aspidochirotida

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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