CHAPTER 20

Triterpene Glycosides from Sea Cucumbers and Their Biological Activities

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Contents

Abstract

Triterpenoid glycosides are abundantly present in sea cucumbers, which are responsible for the toxicity of these echinoderms. More than 100 triterpenoid glycosides have been isolated in the past 20 years and those are grouped into four main structural categories considering their aglycone structure: 3β-hydroxyholost-9(ll)-ene aglycone skeleton, 3β-hydroxyholost-7-ene skeleton, other holostane type aglycones and nonholostane aglycone. Most of the triterpenoid glycosides are found to be possessing potential

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biological activities. Among the biological activities, anticancer activity and antiviral activity are the most widely studied areas. In this communication, we have presented a general view of the structural characteristics of triterpenoid glycosides and their major biological activities. The structural significance and the application limitations of triterpene glycosides are also discussed.

I. INTRODUCTION

Marine organisms have proven to be rich sources of interesting organic molecules. A great number of compounds with diverse structural features and sound biological activities have been reported and reviewed in the literature. Among these, the compounds isolated from sea cucumbers are gaining more attention in the recent past due to their structural features and bioactivities. Sea cucumbers are soft-bodied worm-like echinoderms which belong to the class *Holothuroidea* (De Moncerrat *et al*., 2005). They have economic importance in Asian countries specifically in China where several species are used in traditional medicine or eaten as delicacies. The taxonomical distribution of sea cucumbers consists of six main orders (Apodida, Elasipodida, Aspidochirotida, Molpadiida, Dendrochirotida, and Dacthylochirotida) which include 25 families, about 200 genera, and more than 1400 species. Sea cucumbers can be found in nearly every marine environment but are most diverse on tropical shallow-water coral reefs.

Sea cucumbers gain attention of the scientific crowed in the recent past due to the presence of interesting bioactive compounds with diverse structural features. Therefore, scientists are heavily employed in searching for bioactive compounds from sea cucumbers to be used as potential drugs in the pharmaceutical industry and as neutraceuticals in the food industry. Among the compounds isolated from sea cucumbers, triterpenoid glycosides (saponins) are the major and more interesting. This chapter focuses on the structural features of the triterpenoid glycosides compounds isolated in the recent past and their biological activities.

II. THE STRUCTURAL FEATURES OF TRITERPENE GLYCOSIDES

Triterpene glycosides or triterpene saponins are the most abundant category of secondary metabolites in terrestrial plants. Interestingly, this group of compounds is found to be characteristic metabolites in sea cucumbers. And also these are the predominant secondary metabolites of holothurians, which are presumed to be responsible for their general toxicity (Zhang *et al*., 2006a,b,c,d). More than 100 of triterpene saponins

have been isolated from many species of sea cucumbers belonging to different orders from tropical Pacific, Indian, and Atlantic oceans and the Mediterranean Sea (Antonov *et al*., 2008). Saponins of holothurians are typically composed of carbohydrate and triterpenoid moieties (Kerr and Chen, 1995). The triterpenoid moieties are composed of lanostane derivatives (Zou *et al*., 2005) where majority belongs to holostane type (Dang *et al*., 2007). Holostane type triterpene glycosides include a 3β,20*S*-dihydroxy-5*a*-lanostano-18,20-lactone (**1**) (Fig. 20.1) structural feature. However, recent investigations about these compounds have shown that some triterpene saponins do and those are identified as triterpene saponins with nonholostane aglycone structures. The glycon part of the sea cucumber glycosides is composed of two to six sugar units and it is linked to the C-3 position of the aglycone unit (Chiludil *et al*., 2003; Kalinin *et al*., 2005). Quinovose, glucose, 3-*O*-methylglucose, xylose, and 3-*O*-methylxylose are the only sugars present in the carbohydrate moieties of these glycosides (De Moncerrat *et al*., 2005). In the structure of the oligosaccharide chain, the first monosaccharide unit is always a xylose, while 3-*O*-methylglucose and 3-*O*-methylxylose are always at the terminal. In some glycosides, sulfate groups are attached to the oligosaccharide chain. Most of them are mono-sulfated glycosides with few occurrences of di- and trisulfated glycosides (Chiludil *et al*., 2003).

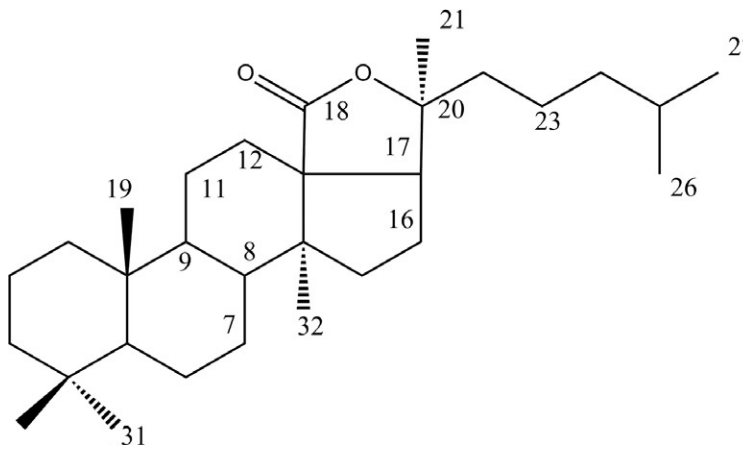


FIGURE 20.1 Structure of the holostane group which is the characteristic aglycone moiety in sea cucumber glycosides.

A. Holostane type sea cucumber glycosides

Reviewing the cited references, the holostane type glycosides were classified into three groups: saponins with 3β-hydroxyholost-9(ll)-ene aglycone skeleton, 3β-hydroxyholost-7-ene skeleton, and saponins contain a aglycone moiety different to above skeletons. Triterpene glycosides with 3β-hydroxyholost-9(ll)-ene aglycone and 3β-hydroxyholost-7-ene skeletons, isolated from different species of sea cucumbers, are listed in Tables 20.1 and 20.2 with their structures illustrated in Figs. 20.2 and 20.3, respectively (Avilov *et al*., 2008).

B. Nonholostane type glycosides

Nonholostane type aglycone moieties are a rare feature in sea cucumber triterpene glycosides. Only few instances have been reported about nonholostane type glycosides. Some of the recently found nonholostane type sea cucumber saponins are listed in Table 20.3 with their structures in Fig. 20.4.

III. BIOACTIVITIES OF TRITERPENE GLYCOSIDES OF SEA CUCUMBERS

Sea cucumbers have long been known for its healing properties and widely used in Chinese traditional medicine rations. Extensive research on this area has revealed that the sea cucumbers gain healing power due to the presence of triterpene glycosides. These compounds exhibit wide spectrum of biological activities such as antifungal, cytotoxic, hemolytic, and immunomodulatory effects (Dang *et al*., 2007; Han *et al*., 2008; Zhang *et al*., 2006c). However, most of the published data demonstrated the anticancer or the cytotoxic activity of triterpene glycosides among the other activities. This suggests that sea cucumber triterpene glycosides are more potent anticancer agents.

A. Anticancer activity

Many natural products have been characterized for the protection against some form of cancer. Sea cucumber triterpenoid glycosides have also been considered as responsible agents for such observations and much research have been conducted to explore the anticancer effect. Most of the triterpene glycosides of sea cucumbers are cytotoxic toward cancer cells. However, their mechanism of anticancer effect has not been elucidated in depth.

TABLE 20.1 Triterpenoid glycosides isolated from different species of sea cucumbers with hydroxyholost-9(ll)-ene aglycone skeleton

Compound name	Species (reference)	Yield (%)	Habitat	Reference
Parvimosides A (**2**)	*Stichopus parvimensis*	8.97×10^{-5}[a]	Monterey, CA	De Moncerrat *et al.* (2005)
Parvimosides B (**3**)		1.45×10^{-4}[a]		
Achlioniceosides A1 (**4**)	*Achlionice violaecuspidata*	0.6×10^{-2}[b]	Weddell sea	Antonov *et al.* (2009)
Achlioniceosides A2 (**5**)		0.8×10^{-2}[b]		
Achlioniceosides A3 (**6**)		0.65×10^{-2}[c]		
Neothyoside A (**7**)	*Neothyone gibbosa*	1.2×10^{-2}[a]	Cerralro, Mexico	Encarnacion *et al.* (1989)
Fuscocineroside A (**8**)	*Holothuria fuscocinera* Jaegar	4.73×10^{-3}[a]	South China	Zhang *et al.*, (2006b)
Fuscocineroside B (**9**)		2.02×10^{-3}[a]		
Fuscocineroside C (**10**)		2.14×10^{-3}[a]		
Pervicoside C (**11**)		6.82×10^{-4}[a]		
Holothurin A (**12**)		6.59×10^{-4}[a]		
Holothurin A3 (**13**)	*Holothuria scabra*	6×10^{-4}[c]	North Vietnam	Dang *et al.* (2007)
Holothurin A4 (**14**)		1.2×10^{-4}[c]		
Holothurins B (**15**)	*Holothuria polii*	1.54×10^{-2}[c]	Italy	Silchenko *et al.* (2005)
Holothurins B2 (**16**)		8.18×10^{-3}[c]		
Holothurins B3 (**17**)		2.73×10^{-3}[c]		
Holothurins B4 (**18**)		2.73×10^{-3}[c]		
Leucospilotaside C (**19**)	*Holothuria leucospilota*	–	South China	Han *et al.* (2008)
DS-penaustrosides C (**20**)	*Pentarta australis* Ludwig	3.16×10^{-4}[a]	Ariake sea	Miyamoto *et al.* (1992)
DS-penaustrosides D (**21**)		6.08×10^{-5}[a]		
Hemoiedemosides A (**22**)	*Hemoiedema spectabilis*	7.53×10^{-3}[a]	Patagonia cost of Argentina	Chiludil *et al.* (2002)

(*continued*)

TABLE 20.1 (*continued*)

Compound name	Species (reference)	Yield (%)	Habitat	Reference
Hemoiedemosides B (**23**)		3.53×10^{-3}[a]		
Marmoroside C (**24**)	*Bohadschia marmorata* Jaeger		South China	Yuan *et al*. (2008)
Fuscocineroside A (**25**)				
Leucospilotaside A (**26**)	*Holothuria leucospilota*	Minor	South China	Han *et al*. (2007)
Two triterpene glycosides (**27**)	*Telenata ananas* sp.	1.9×10^{-4}[a]	Andaman and Nicobar island, India	Hegde *et al*. (2002)
and (**28**)		3.5×10^{-5}[a]		
Arguside A (**29**)	*Bohadschia argus* Jaeger	8.27×10^{-4}[c]	South China	Liu *et al*. (2007)
Arguside B (**30**)	*Bohadschia argus* Jaeger	5.87×10^{-4}[c]	South China	Liu *et al*. (2008b)
Arguside C (**31**)		1.12×10^{-3}[c]		
Arguside D (**32**)	*Bohadschia argus* Jaeger	6.22×10^{-4}[c]	South China	Liu *et al*. (2008a)
Arguside E (**33**)		9.24×10^{-4}[c]		
Impatienside A (**34**)	*Holothuria impatiens*	9.11×10^{-4}[c]	South China	Sun *et al*. (2007)
Bivittoside D (**35**)		6.53×10^{-4}[c]		
17-Dehydroxyholothurinoside A (**36**)	*Holothuria grisea*	3.44×10^{-2}[c]	South China	Sun *et al*. (2008)
Griseaside A (**37**)		6×10^{-4}[c]		
Hillaside C (**38**)	*Holothuria hilla* (**113**)	9.33×10^{-4}[c]	Fujian, China	Wu *et al*. (2006)

[a] Wet weight basis.
[b] Ethanol extractive dry weight basis.
[c] Dry weight basis.

TABLE 20.2 Sea cucumber triterpene glycosides bearing 3β-hydroxyholost-7-ene skeleton

Compound name	Species (reference)	Yield (%)	Habitat	Reference
Eximisoside A (**39**)	*Psolus eximius* Saveljeva	1.92×10^{-3}[a]	Okhotsk sea	Kalinin *et al*. (1997)
Calcigeroside C2 (**40**)	*Pentamera calcigera*	1.76×10^{-4}[a]	Great gulf sea	Avilov *et al*. (2000a)
Okhotoside B1 (**41**)	*Cucumaria okhotensis*	3.83×10^{-4}[a]	Okhotsk sea	Silchenko *et al*. (2008)
Okhotoside B2 (**42**)		5.05×10^{-4}[a]		
Okhotoside B3 (**43**)		4.33×10^{-4}[a]		
Frondoside A (**44**)		3.18×10^{-4}[a]		
Liouvilloside B (**45**)	*Staurocucumis liouvillei*	4.28×10^{-4}[b]	South Georgias island	Maier *et al*. (2001)
Liouvilloside A (**46**)		1.77×10^{-3}[b]		
Liouvilloside A1 (**47**)	*Staurocucumis liouvillei*	2.86×10^{-2}[c]	Sub-Antarctic island of Bouvet	Antonov *et al*. (2008)
Liouvilloside A2 (**48**)		2.32×10^{-2}[c]		
Liouvilloside A3 (**49**)		5×10^{-2}[c]		
Liouvilloside B1 (**50**)		2.5×10^{-2}[c]		
Liouvilloside B2 (**51**)		5.18×10^{-2}[c]		
Patagonicoside A (**52**)	*Psolus patagonicus*	5.42×10^{-3}[c]	Argentina	Murray *et al*. (2001)
Patagonicoside B (**53**)		8.68×10^{-4}[c]		
Synallactoside A1 (**54**)	*Synallactes nozawai*	1.66×10^{-4}[a]	Japan	Silchenko *et al*. (2002)
Synallactoside A2 (**55**)		5.63×10^{-4}[a]		
Synallactoside B1 (**56**)		3.64×10^{-4}[a]		
Synallactoside B2 (**57**)		3.31×10^{-4}[a]		
Synallactoside C (**58**)		7.28×10^{-4}[a]		
Intercedenside A (**59**)	*Mensamaria intercedens*	5×10^{-5}[b]	South China	Zou *et al*. (2003)
Intercedenside B (**60**)		4.2×10^{-5}[b]		
Intercedenside C (**61**)		5.86×10^{-5}[b]		

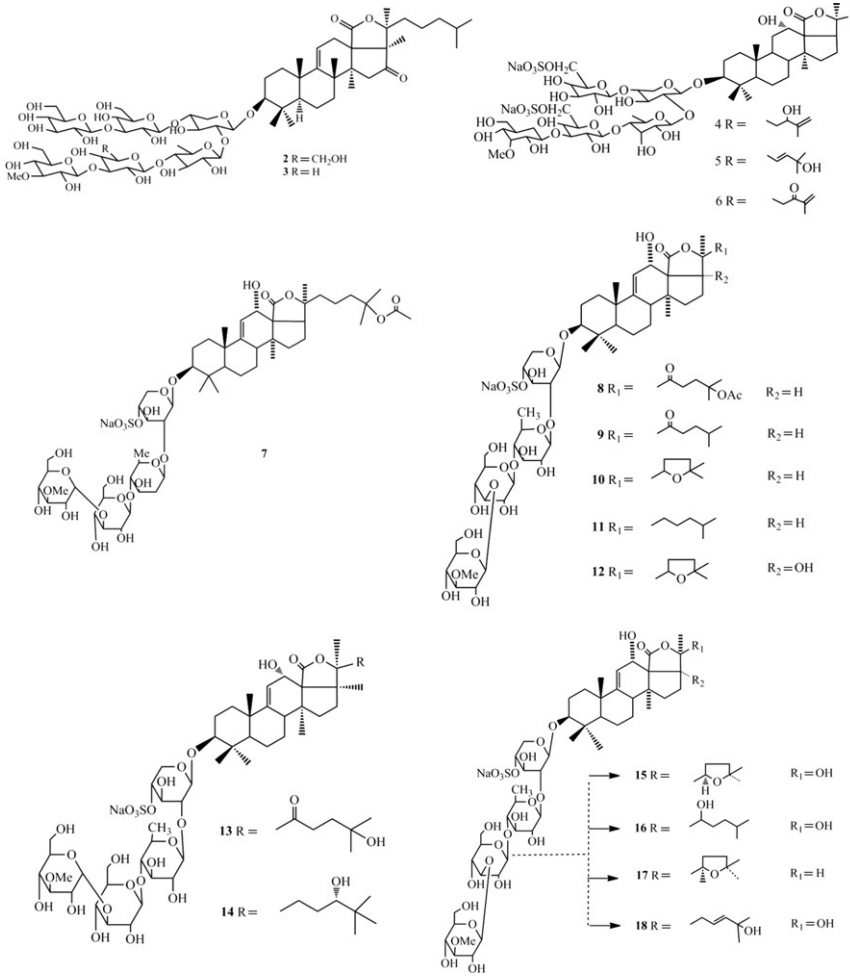
(*continued*)

TABLE 20.2 (*continued*)

Compound name	Species (reference)	Yield (%)	Habitat	Reference
Frondoside B (**62**)	*Cucumaria frondosa*	7.47×10^{-5}[b]	New Brunswick, Canada	Findlay *et al.* (1992)
Frondecaside (**63**)		7.07×10^{-4}[b]		
Lefevreioside A (**64**)	*Cucumaria lefevrei*			
Calcigerosides D2 (**65**)	*Pentamera calcigera*	1.41×10^{-3}[b]	Japan	Avilov *et al.* (2000b)
Cucumariosides A2-5 (**66**)	*Cucumaria conicospermium*	2.18×10^{-3}[b]	Japan	Avilov *et al.* (2003)
Violaceuside A (**67**)	*Pseudocolochirus violaceus*	1.68×10^{-4}[b]	South China	Zhang *et al.* (2006c)
Violaceuside B (**68**)		3×10^{-5}[b]		
Violaceuside I (**69**)	*Pseudocolochirus violaceus*	2.83×10^{-5}[b]		Zhang *et al.* (2006d)
Violaceuside II (**70**)		7×10^{-5}[b]		
Violaceuside III (**71**)		4.67×10^{-5}[b]		
Philinopside A (**72**)	*Pentacta quadrangularis*	2.46×10^{-3}[a]	South China	Yi *et al.* (2006)
Philinopside B (**73**)		1.26×10^{-3}[b]		Zhang *et al.* (2006c)
Philinopside E (**74**)	*Pentacta quadrangularis*	5.46×10^{-4}[a]	South China	Zhang *et al.* (2006a)
Philinopside F (**75**)		1.62×10^{-4}[a]		
Pseudostichoposide B (**76**)	*Pseudostichopus trachus*		North Pacific	Silchenko *et al.* (2004)
Pseudostichoposide A (**77**)				
Intercedenside B (**78**)	*Pseudocolochirus violaceus*	9.17×10^{-5}[b]	South China	Zhang *et al.* (2007)
Okhotoside $Ä_1$-1 (**79**)	*Cucumaria okhotensis*	4.33×10^{-5}[c]	Kamchatka	Silchenko *et al.* (2007)
Okhotoside $Ä_2$-1 (**80**)		4.33×10^{-5}[c]		
Okhotoside $Ä_0$-1 (**81**)		7.22×10^{-5}[c]		

[a] Dry weight basis.
[b] Wet weight basis.
[c] Ethanol extractive dry weight basis.

The *in vitro* cytotoxicity of five triterpene glycosides, fuscocineroside A (**8**), B (**9**), and C (**10**), pervicoside C (**11**), and holothurin A (**12**) isolated from *Holothuria fuscocinerea* Jaeger on human leukemia HL-60 and human hepatoma BEL-7402 cells, was analyzed, and all compounds have shown a potent cytotoxicity in both cell lines. However, compound 10 was found to be the most potent (IC_{50}=0.88 and IC_{50}=0.58 μg/ml) in HL-60 and BEL-7402 cell lines, respectively (Zhang *et al*., 2006d). The triterpene glycosides from the sea cucumber *Holothuria scabra*, namely, holothurin A3 (**13**) and A4 (**14**), were found to be strongly cytotoxic to cancer cell lines, human



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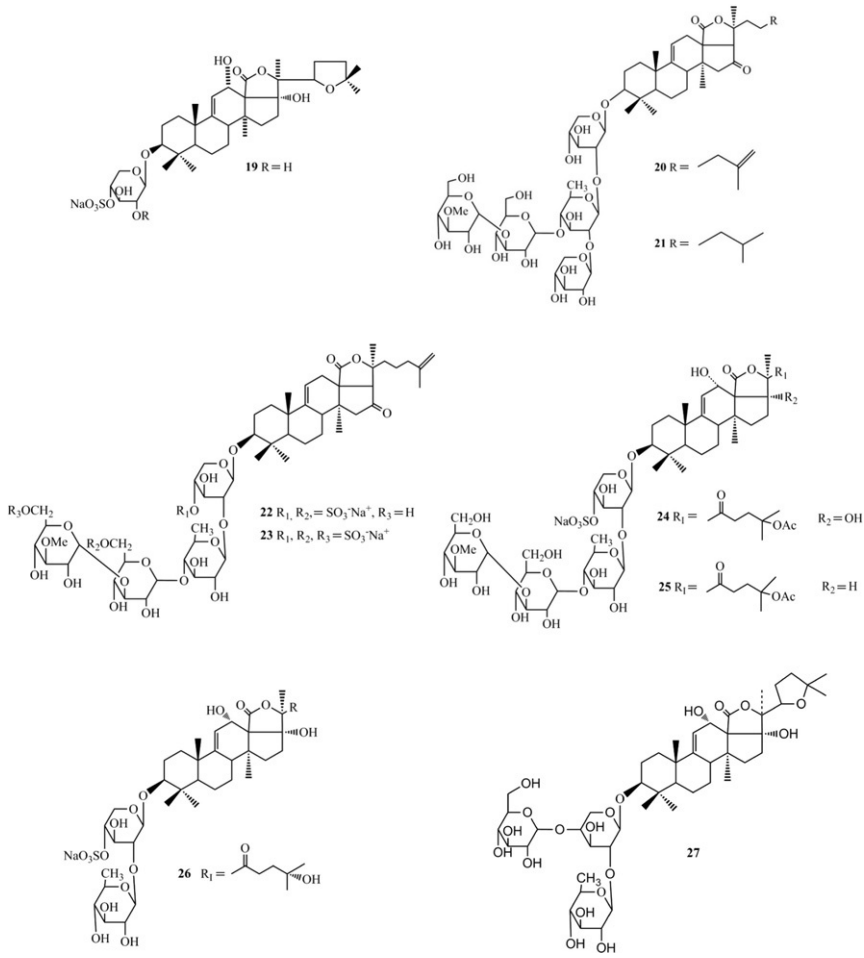


epidermoid carcinoma (KB) and human hepatocellular carcinoma (HepG2), with IC_{50} values of 0.87 and 0.32 μg/ml (for compound **13**) and of 1.12 and 0.57 μg/ml (for compound **14**), respectively (Dang *et al.*, 2007). Argusside A (**29**) also exhibited significant cytotoxicity against different human tumor cell lines, while showing the highest activity toward human colorectal carcinoma (HCT-116) cells (IC_{50}=0.14 μM) with more potency than the employed positive control, 10-hydroxycamptothecin (HCP) (IC_{50}=0.84 μM) (Liu *et al.*, 2007). Argusides B (**30**) and C (**31**) have also shown potent cytotoxicity against human tumor cell lines, adenocarcinomic human alveolar basal epithelial cells (A549) and HCT-116 in

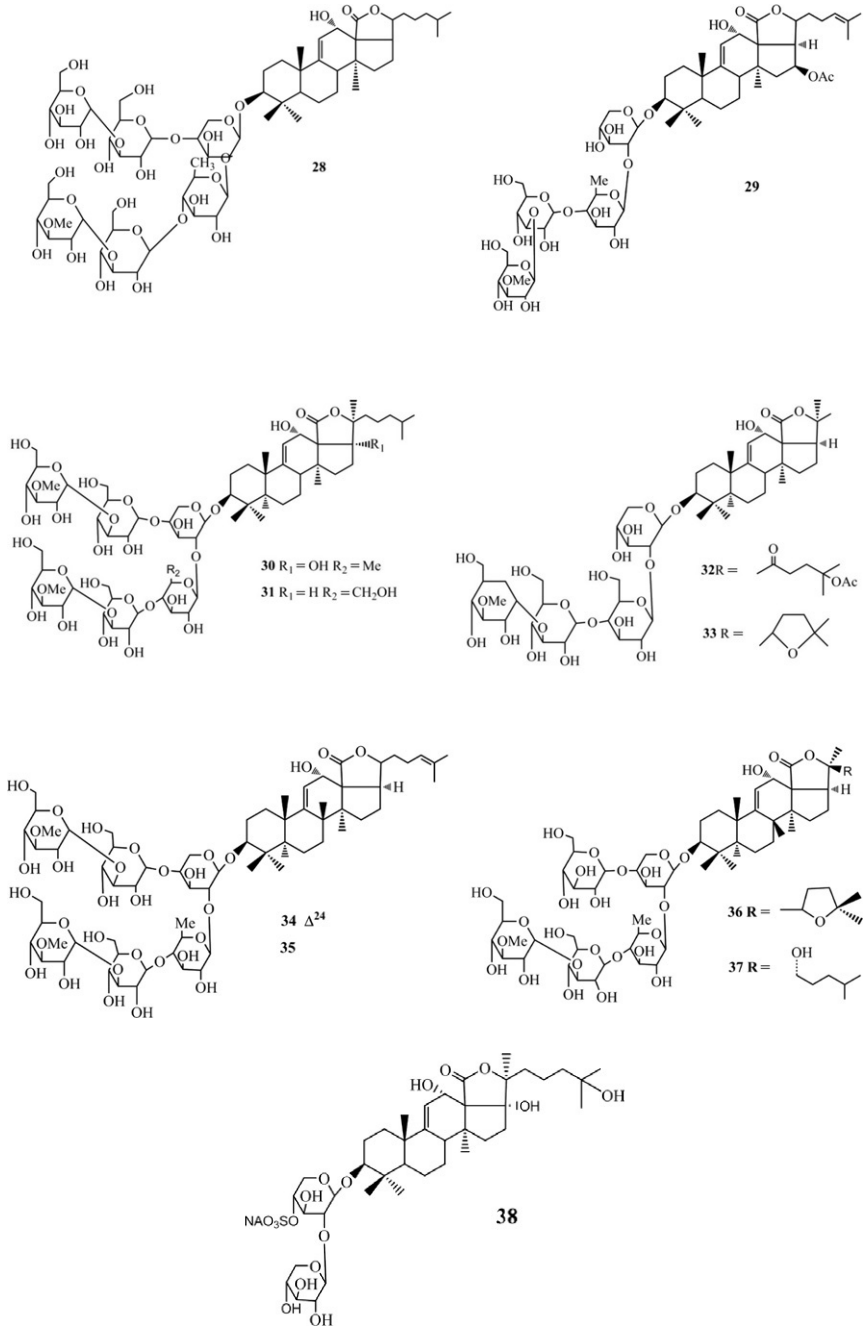
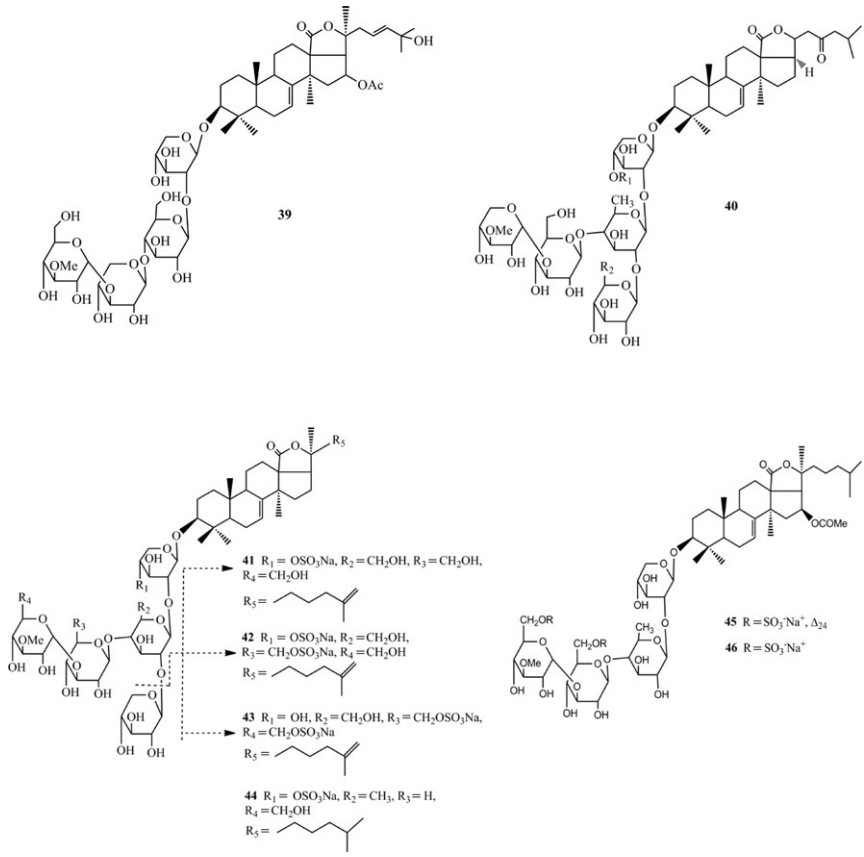


FIGURE 20.2 Triterpenoid glycosides isolated from sea cucumbers, having 3β-hydroxyholost-9(ll)-ene aglycone skeleton.



HepG2, and human breast adenocarcinoma (MCF-7) cell lines. The cytotoxicity of the compounds on A549 (**30**-IC_{50}: 0.48 μg/ml, **31**-IC_{50}: 0.43 μg/ml) and HCT-116 (**30**-IC_{50}: 0.46 μg/ml, **31**-IC_{50}: 0.38 μg/ml) cells was more potent than the positive control V-16. However, there was no significant difference between the cytotoxicities of 38 and 39 (Liu *et al*., 2008b). Besides, argusides D (**32**) and E (**33**) have also been tested for their anticancer activities in above human cancer cell lines and revealed a significant activity with IC_{50} values in the range of 3.36–7.77 μg/ml (Liu *et al*., 2008a). However, the activity is comparatively lower to the compounds **30** and **31**. This finding clearly indicates that the length and type of sugar moieties of glycosides play an important role in terms of cytotoxic activity against tumor cells. Moreover, the *in vitro* cytotoxicities of impatienside A (**34**) and bivittoside D (**35**) were evaluated extensively for

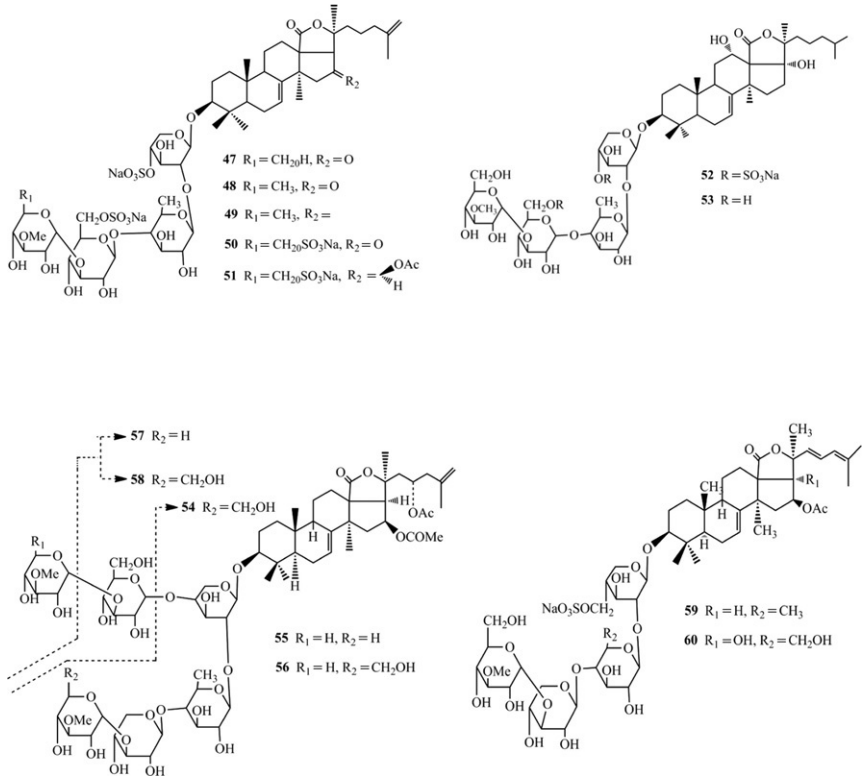
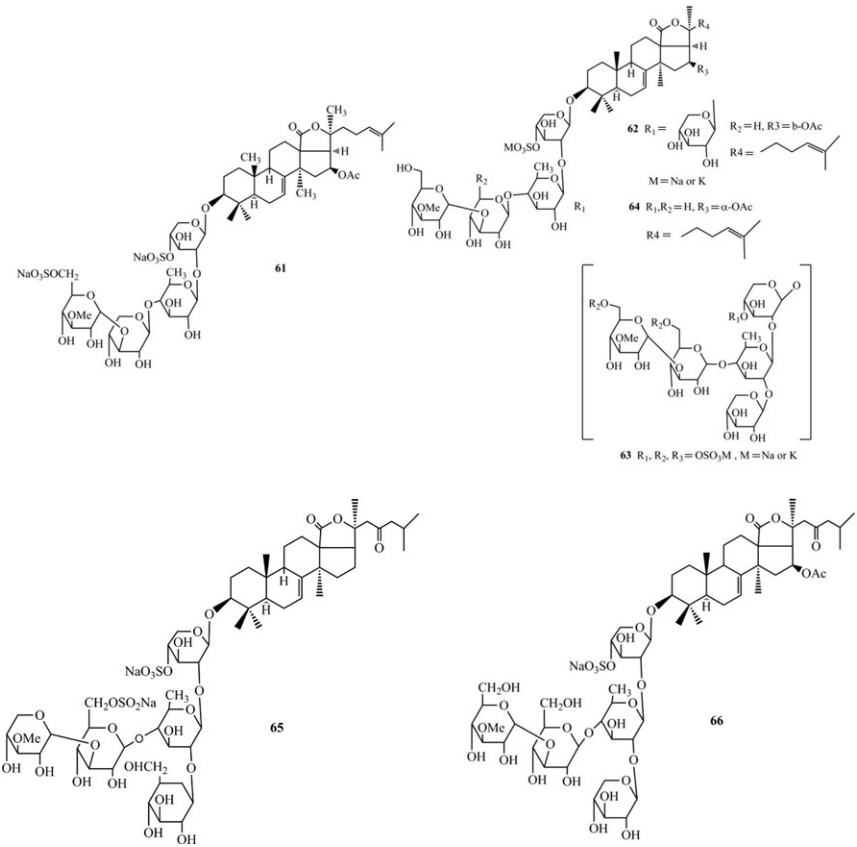


Figure 20.3 (Continued)

cytotoxicity by employing seven human cancer cell lines and the results indicate that both glycosides exhibited *in vitro* cytotoxicities similar to or better than that of the potent anticancer drug etoposide (V-16) in four human tumor cells, A549 (**34**-IC_{50}: 0.35 μg/ml, **35**-IC_{50}: 0.52 μg/ml), HCT-116 (**34**-IC_{50}: 0.45 μg/ml, **35**-IC_{50}: 0.37 μg/ml), DU-145 (**34**-IC_{50}: 1.14 μg/ml, **35**-IC_{50}: 0.937 μg/ml), and KB (**34**-IC_{50}: 1.6 μg/ml, **35**-IC_{50}: 1.42 μg/ml) (Sun *et al.*, 2007). The structural differences between glycosides **34** and **35** were limited to their holostane skeleton, and there was no significant difference in the cytotoxicities of the two glycosides. However, pervicoside C (**11**), an analogue of **35** having the same aglycone but a different sugar chain, isolated from *H. fuscocinerea* Jaeger, exhibited weak activities against HCT-116 and A549 cancer cells, with IC_{50} values of 18.7 and 28.6 μg/ml, respectively (Sun *et al.*, 2007). According to these results, it could be suggested that the length and type of sugar moieties of such glycosides play an important role in terms of cytotoxic activity against tumor cells.



17-Dehydroxyholothurinoside A (**40**) and griseaside A (**41**) are identified as promising anticancer agents due to their significantly higher cytotoxicity against four human tumor cell lines, A549 (**40**-IC_{50}: 0.886 μM, **41**-IC_{50}: 1.07 μM), HL-60 (**40**-IC_{50}: 0.245 μM, **41**-IC_{50}: 0.427 μM), BEL-7402 (**40**-IC_{50}: 0.97 μM, **41**-IC_{50}: 1.114 μM), and human acute lymphoblastic leukemia cell line (Molt-4) (**40**-IC_{50}: 0.34 μM, **41**-IC_{50}: 0.521 μM) compared to the positive control HCP (A549 IC_{50}: 2.35 μM, BEL-7402 IC_{50}: 2.6 μM, HL-60 IC_{50}: 1.9 μM, Molt-4 IC_{50}: 2.2 μM) (Sun *et al.*, 2008). Hillaside C (**38**) has also been tested for its anticancer potential against eight human tumor cell lines (A-549, MCF-7, human lung carcinoma cells—IA9, human clear cell carcinoma cells—CAKI-1, human prostate cancer cells—PC-3, KB, KB-VIN, and human colorectal adenocarcinoma cells—HCT-8) and has exhibited cytotoxicity with IC_{50} values in the range of 0.15–3.20 μg/ml (Wu *et al.*, 2006). Compared to the positive control HCP, the compound **38**

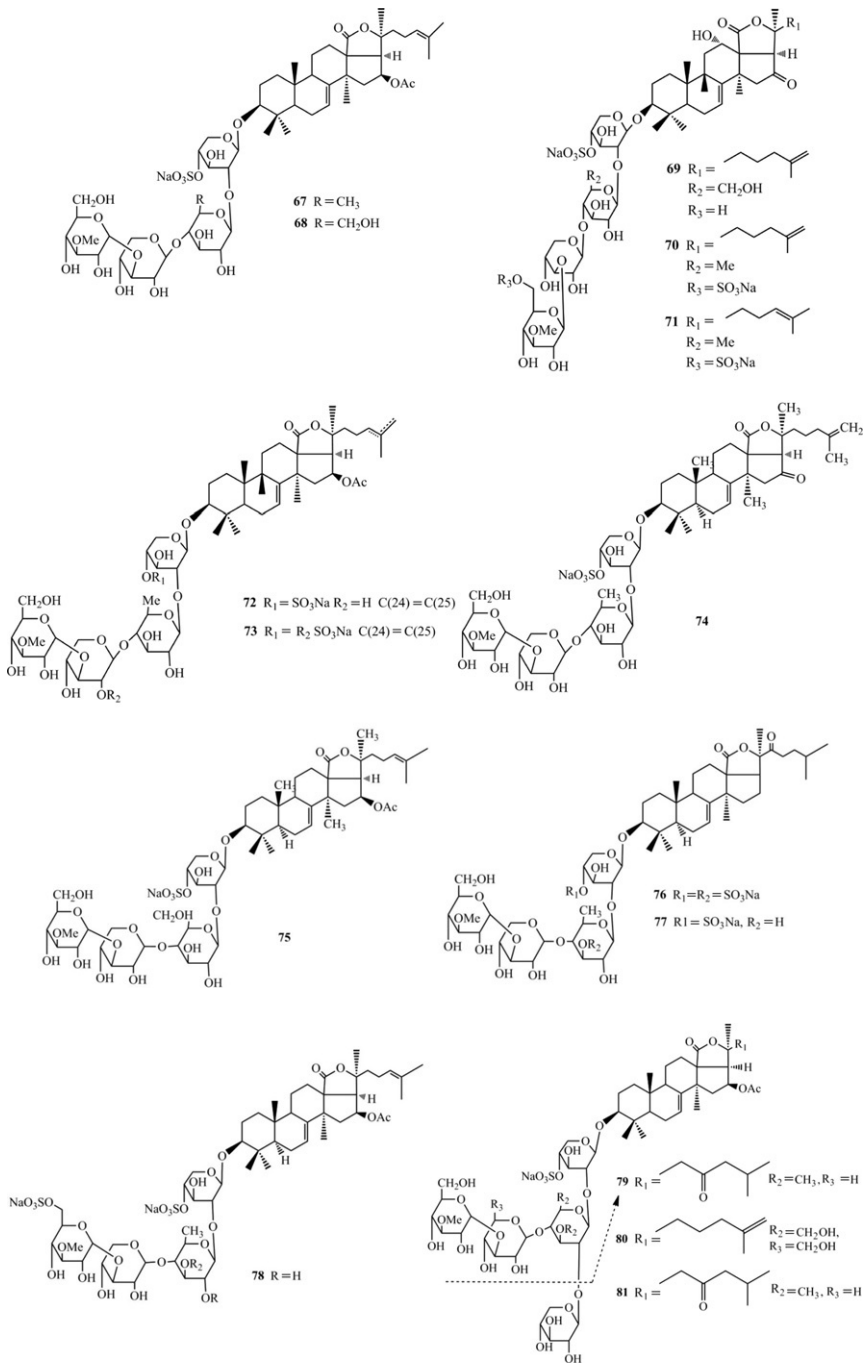


FIGURE 20.3 Triterpenoid glycosides isolated from sea cucumbers, having 3β-hydroxyholost-7(8)-ene aglycone skeleton.

TABLE 20.3 Nonholostane type triterpene glycosides isolated from sea cucumbers

Compound name	Species (reference)	Yield (%)	Habitat	Reference
Calcigerosides B (**82**)	*Pentamera calcigera*	1.76×10^{-2}[a]	Great gulf sea	Zou *et al.* (2006)
Calcigerosides C1 (**83**)		1.76×10^{-4}[a]	Japan	
Cucumarioside G2 (**84**)		6.35×10^{-2}[a]		
Koreoside A (**85**)	*Cucumaria koraiensis*	5×10^{-3}[b]	Kurile island	Avilov *et al.* (1997)
DS-penaustrosides A (**86**)	*Pentarta australis* Ludwig	4.27×10^{-4}[b]	Ariale sea	Miyamoto *et al.* (1992)
DS-penaustrosides B (**87**)		1.29×10^{-4}[b]		
Calcigerosides D1 (**88**)	*Pentamera calcigera* Stimpson	2.82×10^{-2}[a]	Peter the Great gulf	Avilov *et al.* (2000a)
DS-calcigeroside D1 (**89**)				

[a] Dry weight basis.
[b] Wet weight basis.

has shown more potent cytotoxicity toward CAKI-1 (**42**-IC_{50}: 0.15 μg/ml) and KB-VIN (**42**-IC_{50}: 2.81 μg/ml) cell lines. Three new triterpene glycosides, intercedensides A (**59**), B (**60**), and C (**61**) from *Mensamaria intercedens* Lampert, were widely studied for their anticancer activity employing 10 human tumor cell lines (A549, MCF-7, IA9, CAKI-1, human glioblastoma cells: U-87-MG, PC-3, KB, KB-VIN, human skin melanoma cells: SK-MEL-2, HCT-8). Interestingly, all compounds showed a significant cytotoxicity against all tumor cell lines within the IC_{50} value range of 0.7–4 μg/ml, and the compounds **59** and **61** showed similar potencies, while compound **60** was generally more potent in all cell lines. Further, **59** also exhibited significant *in vivo* antineoplastic activity against mouse Lewis lung cancer and mouse S180 sarcoma, with 48.39% and 57.48% reduction levels (Zou *et al.*, 2003).

New sulfated triterpene glycoside from *Pentacta quadrangularis*, philinopside E (**74**), showed a significant cytotoxicity (IC_{50}: 0.75–3.50 μg/ml) against 10 tumor cell lines (mouse lymphocytic leukemia cells: P388,

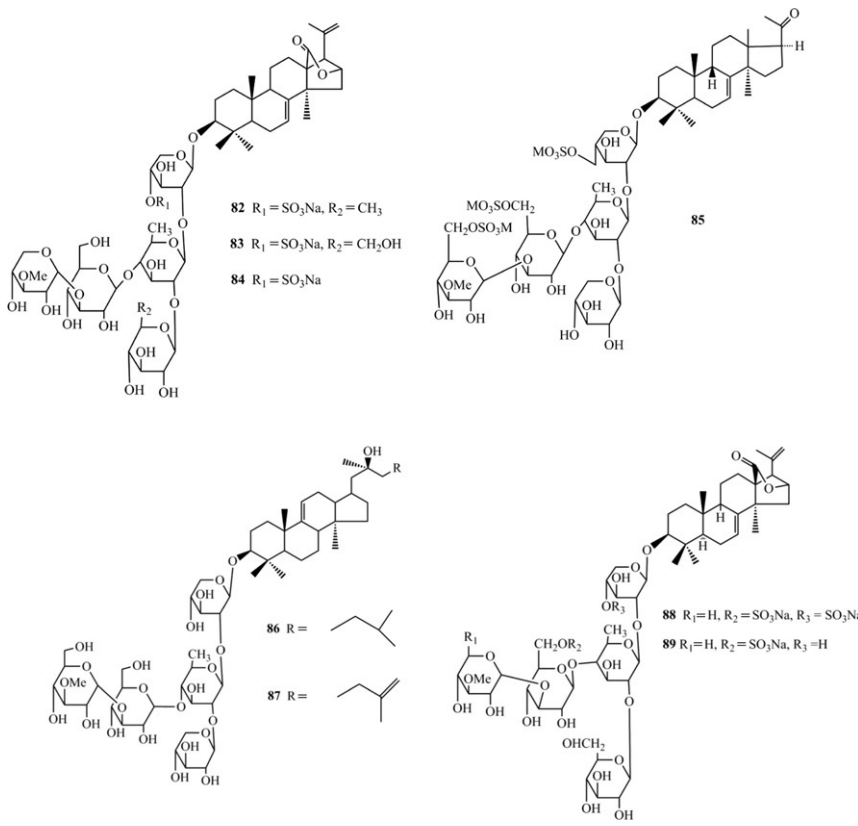


FIGURE 20.4 Triterpenoid glycosides isolated from sea cucumbers having nonholostane type aglycone moiety.

HL-60, A549, lung adenocarcinoma cells: SPC-A4, gastric carcinoma cells: MKN28, gastric carcinoma cells: SGC7901, BEL-7402, human ovarian carcinoma: HO8901, human fetal lung fibroblasts: W138, human epithelial carcinoma cells: A431) (Zhang *et al.*, 2006b). Further, sulfated triterpene glycoside, **78** from *Pseudocolochirus violaceus*, exhibited significant cytotoxicity against cancer cell lines MKN-45 (human gastric adenocarcinoma) and HCT-116 with IC_{50} values in the range of 0.052–0.442 μM, and both compounds showed significantly higher activity against HCT-116 compared to the positive control HCP (Zhang *et al.*, 2007). Moreover, the sulfated triterpene glycosides, philinopsides A (**72**) and B (**73**), showed significant cytotoxicity (IC_{50}: 0.75–3.50 μg/ml) against 10 tumor cell lines (CAKI, HOS, KB-VIN, KB, SM-MEL-2, U87-MG, HCT-8, IA9, A549, and PC3) (Yi *et al.*, 2006). Collectively, all these triterpene glycosides of

sea cucumber are very potent cytotoxic agents toward a wide array of cancer types. Detailed studies on the anticancer effects of these compounds are needed to confirm their activity and use them as anticancer therapeutics.

B. Antifungal activity

Antifungal activity is the second most studied biological activity of sea cucumber triterpene glycosides and their polar extracts. Some triterpene glycosides had shown pronounced activity where they have been effective against some fungal strains than commercially available fungicides in a concentration-dependent manner. Polar fraction of the crude extracts of the sea cucumber *Holothuria polii* exhibited a significant antifungal activity in a concentration-related manner (150–300 μg/well) where the strains of *Aspergillus fumigatus* were more susceptible (Ismail *et al.*, 2008). And also the crude methanolic extract of *Actinopyga lecanora* have showed significant antifungal activity against *Candida albicans* (MIC, 62.5 μg/ml), *Candida neoformans* (MIC, 125 μg/ml), *Sporothrix schenckii* (MIC, 62.5 μg/ml), *Trichophyton mentagrophytes* (MIC, 125 μg/ml), and *A. fumigatus* (MIC, 31.2 μg/ml) (Kumar *et al.*, 2007). Sea cucumber triterpene glycoside, holothurin B (**15**) isolated from *A. lecanora*, showed an excellent antifungal activity by acting against 20 test fungal isolates. It has been reported that the activity of holothurin B is more effective than standard antifungal agent fluconazole when tested against *T. mentagrophytes* (MIC range of 1.56 μg/ml), and it has showed a comparable activity to fluconazole against *S. schenckii* and *A. fumigatus* (Kumar *et al.*, 2007). Hemoiedemosides A (**22**) and B (**23**) isolated from sea cucumber *Hemoiedema spectabilis* have been exhibited a considerable antifungal activity against the phytopathogenic fungus *Cladosporium cucumerinum*. It has been found that the disulfated glycoside (**22**) was more active than commercial antiviral agent benomyl at the higher concentrations (20–50 μg/spot) (Chiludil *et al.*, 2003). However, hemoiedemoside B (**23**), differing from hemoiedemoside A in the presence of a third sulfate group at C-6‴″, is less active than hemoiedemoside A. Patagonicoside A (**52**), a disulfated tetraglycoside isolated from the holothuroid *Psolus patagonicus*, have also shown antifungal activity against the fungus, *C. cucumerinum* in a concentration-dependent manner (1.5–50 μg/spot). Also in this study, the desulfated derivative of patagonicoside A showed marked reduction in the antifungal activity (Murray *et al.*, 2001). In latter two studies, the lesser active desulfated derivatives differ only by their sulfate substitutions in the glycon part of the structure. Therefore, it can be suggested that the presence of sulfate groups in the oligosaccharide chain plays an important role with regard to the antifungal activity of the triterpene glycoside.

Moreover, the antifungal effects of patagonicoside A (**52**) and hemoiedemoside A (**23**) were compared using a phytopathogenic fungus *C. cucumerinum*. It has been found that patagonicoside A was less active than the hemoiedemoside A at the same concentrations. Both glycosides contain the same oligosaccharide chain and a triterpenoid aglycone with an 18 (20)-lactone. However, patagonicoside A contains a Δ^7 double bond and two hydroxyl functions at C-12 (R) and C-17 (R) in its aglycone part where hemoiedemoside A has Δ^{11} double bond position. Therefore, it could also be suggested that differences in the antifungal activity could be due to structural differences in the aglycone unit (Chiludil *et al*., 2002).

IV. STRUCTURE–ACTIVITY RELATIONSHIPS

The structure–activity relationships of sea cucumber triterpene glycosides have not been extensively studied; however, several reviews have suggested the structural relationships to their activities exerted. As suggested by many authors, the bioactivity of the triterpene glycosides is a resultant of its strong membranolytic activity. And this membranolytic activity is a function of the structural feature of the glycoside (Kalinin, 2000). The presence of an 18(20)-lactone as the aglycone with at least one oxygen group near it has critical significance for biological activity of glycosides bearing 9(11)-double bond (Kitagawa, 1988). Glycosides with a 7(8)-double bond in their aglycone structure with absence of 16-ketogroup are more active than those with presence of a 16-ketogroup (Kalinin *et al*., 1996). The characteristics of the attached glycon structure are also critical for the bioactivities of the sea cucumber triterpene glycosides. It has been found that for the actions leading to modification of the cellular membrane, a linear tetrasaccharide chain is significant (Kalinin *et al*., 1992; Kitagawa, 1988). And also Maltsev *et al*. (1985) have reported that glycosides having quinovose as a second monosaccharide unit are more active over others. The sulfation of the sugar chain is also a significant factor related to bioactivity. A sulfate group at C-4 of the first xylose residue increases the effect against membranes. The absence of a sulfate group at C-4 of the xylose residue in biosides decreases its activity from more than onefold magnitude. However, the presence of a sulfate at C-4 of the first xylose in branched pentanosides having 3-*O*-methyl group as a terminal monosaccharide increases activity. However, the same sulfate can decrease the activity of branched pentanosides, which are having glucose as the terminal residue. And sulfate groups attached to a C-6 position of terminal glucose and 3-*O*-methylglucose residues impart a great reduction in the activity (Kalinin, 2000).

V. PROS AND CONS IN DRUG DEVELOPMENT FROM SEA CUCUMBERS

Up to date, the vast diversity of sea cucumbers paved way for natural product chemists to mine for new bioactive compounds. Among them, sea cucumber triterpene glycosides are the most studied. Similar to that in other marine invertebrates, survival demand has resulted in the evolution of these sophisticated toxic compounds and this fact is confirmed by the proved toxicity of these compounds in biochemical studies. Holothurians are used as ingredients for traditional Chinese medicine for years. And also, holothurin A is marketed in Japan as an ingredient in an antifungal medicine. Even though there are many lead compounds with promising potential to be used as drugs for cancer therapy, the cytotoxicity itself would be a constrain for this purpose, because most of the compounds could be cytotoxic toward normal cells in addition to the cancerous cells. However, in finding therapeutics from natural products, always the preference is given to the compounds having high specificity toward the cancer cells in their cytotoxic action, while minimizing the damage to normal cells. Therefore, considerable cytotoxic studies should be conducted employing the lead compounds before introducing them to the drug development phase. Moreover, the possibility of continuous supply of the product and the ecological importance of the sea cucumber are factors of importance before entering to the drug development phase. However, it is undoubtedly possible to develop new drugs from these interesting natural products of sea cucumbers with extensive research on their activity and toxicity.

VI. CONCLUDING REMARKS

Sea cucumbers can be utilized maximally in the research areas of new drug developments, specifically in the area of anticancer. Due to proven anticancer effects, several triterpenoid glycosides could be potential candidates for development of new drugs. However, the mechanisms of the activity with structure–activity relationship should be studied more, as there is considerable gap in this area compared with isolation rate of new compounds. And also adequate clinical trials are needed in drug development, since the bioactive triterpenoid compounds bares a high cytotoxic potential. And also the mode of the drug delivery into the body should be clearly studied due to the above reason.

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