

Review

Sea Cucumber Glycosides: Chemical Structures, Producing Species and Important Biological Properties

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Received: 27 June 2017; Accepted: 11 October 2017; Published: 17 October 2017

Abstract: Sea cucumbers belonging to echinoderm are traditionally used as tonic food in China and other Asian countries. They produce abundant biologically active triterpene glycosides. More than 300 triterpene glycosides have been isolated and characterized from various species of sea cucumbers, which are classified as holostane and nonholostane depending on the presence or absence of a specific structural unit $\gamma(18,20)$ -lactone in the aglycone. Triterpene glycosides contain a carbohydrate chain up to six monosaccharide units mainly consisting of D-xylose, 3-O-methy-D-xylose, D-glucose, 3-O-methyl-D-glucose, and D-quinovose. Cytotoxicity is the common biological property of triterpene glycosides isolated from sea cucumbers. Besides cytotoxicity, triterpene glycosides also exhibit antifungal, antiviral and hemolytic activities. This review updates and summarizes our understanding on diverse chemical structures of triterpene glycosides from various species of sea cucumbers and their important biological activities. Mechanisms of action and structural–activity relationships (SARs) of sea cucumber glycosides are also discussed briefly.

Keywords: holostane; nonholostane; cucumarioside; cytotoxic; antifungal; glycosides

1. Introduction

Nature is the largest source of pharmaceutical lead drugs for the remedies of many diseases. Earlier scientists mainly focused on terrestrial samples (plants and microorganisms) for the discovery of lead bioactive compounds. With the passage of time, the search for new drugs or agrochemicals has been switching from land to ocean due to re-isolation of known natural products from terrestrial samples. Marine organisms produce diversified bioactive compounds because of large species biodiversities and living in extremely harsh environment.

Among so many sources, numerous bioactive metabolites have been isolated from marine invertebrates such as echinoderms with a broad spectrum of biological activities [1]. The echinoderms are divided into five classes, i.e., Holothuroidea (sea cucumbers), Asteroidea (starfishes), Echinoidea (sea urchins), Crinoidea (sea lilies), and Ophiuroidea (brittle stars and basket stars), which live exclusively in the marine habitat, distributed in almost all depths and latitudes, as well as reef

environments or shallow shores [2,3]. The importance of these echinoderms as a potential source of bioactive compounds for the development of new therapeutic drugs/agrochemicals has been growing rapidly [1]. Compounds isolated from echinoderms showed numerous biological activities including antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, anti-tuberculosis, anti-inflammatory, antitumor, and antiviral activities [1].

Sea cucumber traditionally has been used as tonic food in China and other Asian countries for thousands of years. Besides being used as food, sea cucumbers are also promising source of bioactive natural products which predominantly belong to triterpene glycosides exhibiting antifungal, cytotoxic, hemolytic, cytostatic, and immunomodulatory and antiviral activities [4]. Several monographs concerning the structures and biological properties of triterpene glycosides obtained from sea cucumbers have been published but not presented in a systematic way [5,6]. This report comprehensively reviews in depth structural features of sea cucumber glycosides with corresponding producing species. Important biological activities, mechanism of action, and structure–activity relationships (SARs) of the diverse glycosides produced by the different species of sea cucumber are also discussed briefly.

2. Taxonomy, Distribution and Nutritive Value of Sea Cucumbers

One of the predominant invertebrate lives in marine environment is sea cucumber, which belong to the class Holothuroidea under the phylum Echinodermata. Holothuroidea has been divided into three subclasses, Aspidochirotea, Apodacea and Dendrochirotea, and further into six orders, Apodida, Elaspodida, Aspidochirotida, Molpadida, Dendrochirotida and Dactylochirotida [7]. Majority of the harvestable species of sea cucumbers belong to three families, viz., Holothuriidae (genera *Holothuria* and *Bohadschia*), Stichopodidae (genera *Stichopus*, *Actinopyga*, *Thelenota*, *Parastichopus* and *Isostichopus*), and Cucumariidae (genus *Cucumaria*) [8].

Sea cucumbers are elongated tubular or flattened soft-bodied marine benthic invertebrates, typically with leathery skin, ranging in length from a few millimeters to a meter [9]. Holothuroids encompass 14,000 known species occur in most benthic marine habitats worldwide, in both temperate and tropical oceans, and from the intertidal zone to the deep sea, and are considered as the very important parts of oceanic ecosystem [10].

Economically, sea cucumbers are important in two reasons: first, some species produce triterpene glycosides that are interested to pharmaceutical companies finding their medical use and second, use as food item. About 70 species of sea cucumbers have been exploited worldwide; out of which 11 species have been found to be commercially important [11]. Sea cucumbers have been well recognized as a tonic and traditional remedy in Chinese and Malaysian literature for their effectiveness against hypertension, asthma, rheumatism, cuts and burns, impotency and constipation [12,13]. Nutritionally, sea cucumbers have an impressive profile of valuable nutrients such as vitamin A, vitamin B₁ (thiamine), vitamin B₂ (riboflavin), vitamin B₃ (niacin), and minerals, especially calcium, magnesium, iron and zinc [14,15].

3. Extraction, Purification and Characterization

To extract glycosides, first sea cucumbers will be freeze dried, then cut into pieces and extracted twice with refluxing EtOH. The combined extracts will be concentrated under reduced temperature and the residue will be dissolved in H₂O. Desalting will be carried out by passing this fraction through a Polychrom column (Teflon), eluting first the inorganic salts and crude polar impurities with H₂O and then the glycosides fraction with 50% EtOH. The fraction will be sub-fractionated by silica gel column chromatography using suitable gradient solvent system. The glycosides from each sub-fraction can be purified by reverse phase HPLC developing suitable solvent system (MeOH-H₂O).

Triterpene glycosides have two parts: carbohydrate and triterpene. The number of monosaccharide units present in the carbohydrate chain can be deduced by observing the number of anomeric carbons (~103 ppm) and protons (~5 ppm, d) resonances in ¹³C and ¹H NMR spectra, respectively. The sequence

of monosaccharide units in the carbohydrate chain can be established by the analysis of anomeric H/C correlations in the HMBC spectrum which can also be confirmed by NOE correlations between anomeric protons and MALDI-TOF mass spectroscopic data analysis. The position of attachment of glycone with aglycone can be confirmed by the HMBC experiment.

The presence of diverse types of monosaccharide units and their repetitions in the carbohydrate chain can be established by acid hydrolysis followed by GC-MS analysis of the corresponding aldonitrile peracetates [16]. The site of attachment of sulfate group at monosaccharide units can be determined by observing chemical shift of esterification carbon atoms. The chemical shifts of α (esterification) and β -carbons are shifted ~ 5 ppm downfield and ~ 2 ppm up field, respectively, compare to their corresponding nonsulfated derivatives.

The structure of the aglycone can be established based on its spectroscopic data (^1H NMR, ^{13}C NMR, COSY, HMBC, HSQC, and TOCSY) and by comparing with the literature data. Configuration can be determined by the analysis of NOE data, stable conformers, coupling constants and comparing chemical shifts of chiral centers with literature.

4. Structural Features of Triterpene Glycosides Isolated from Sea Cucumbers

Triterpene glycosides, also known as holothurins or saponins, are secondary metabolites typically produced by sea cucumbers (class Holothuroidea). These glycosides are amphiphilic in nature having two parts: aglycone (lipophilic, lipid-soluble) and glycone (hydrophilic, water-soluble). The majority of the glycosides contain so called holostane type aglycone comprise of lanostane- 3β -ol with a $\gamma(18,20)$ -lactone in the E-ring of the pentacyclic triterpene [($3\beta,20S$ -dihydroxy- 5α -lanostano- $\gamma(18,20)$ -lactone)] (Figure 1). A few of the glycosides contain nonholostane type aglycone which do not have $\gamma(18,20)$ -lactone in the tetracyclic triterpene.

The glycone parts may contain up to six monosaccharide units covalently connected to C-3 of the aglycone. The sugar moieties mainly consist of D-xylose (Xyl), D-quinovose (Qui), D-glucose (Glc), 3-O-methyl-D-glucose (MeGlc), 3-O-methyl-D-xylose (MeXyl) (Figure 2) and sometimes 3-O-methyl-D-quinovose (MeQui), 3-O-methyl-D-glucuronic acid (MeGlcA) and 6-O-acetyl-D-glucose (AcGlc). In the carbohydrate chain, the first sugar unit is always a xylose and a majority case second is quinovose, whereas 3-O-methyl-D-glucose and/or 3-O-methyl-D-xylose are always the terminal monosaccharide units. The presence of two quinovose residues in a carbohydrate chain is unique for sea cucumber and starfish glycosides.

In glycone part, the sugar units are generally arranged in a straight or branched chain (Figure 3). The majority of tetrasaccharides show a linear chain with the most common 3-O-Me-Glc-(1 \rightarrow 3)-Glc-(1 \rightarrow 4)-Qui-(1 \rightarrow 2)-Xyl. Hexaglycosides are generally nonsulfated with a linear 3-O-Me-Glc (1 \rightarrow 3)-Glc (1 \rightarrow 4)-Xyl (2 \rightarrow 1)-Qui (4 \rightarrow 1)-Glc (3 \rightarrow 1)-3-O-MeGlc unit. Pentasaccharides have a linear chain like tetrasaccharides but a branching at C-2 of quinovose (Figure 3).

Sixty percent of the triterpene glycosides isolated so far from sea cucumbers have sulfate groups linked to the monosaccharide units of the carbohydrate chain. Most of them are monosulfated, but many di- and trisulfated glycosides have also been isolated. Most tetrasaccharides and pentasaccharides are sulfated at C-4 of xylose unit. In both the cases, additional sulfate groups at C-6 of the 3-O-methylglucose and glucose units have also been found. The term "Ds" stands for desulfated. Sea cucumber triterpene glycosides are chemotaxonomic markers specific for groups of genera within each family.

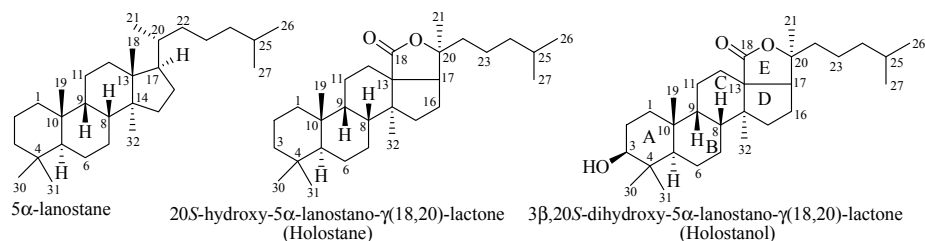


Figure 1. Structures of lanostane, holostane and holostanol.

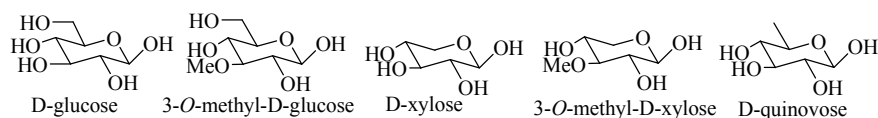


Figure 2. Common sugar units present in sea cucumber glycosides.

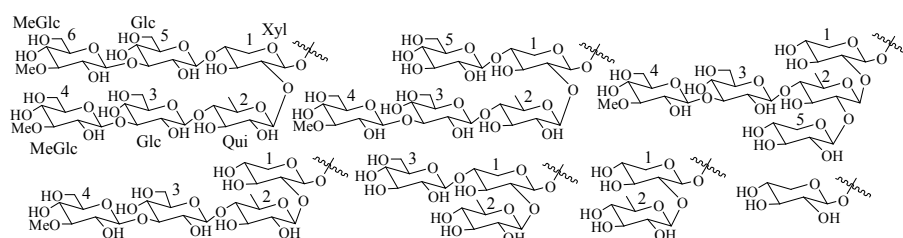


Figure 3. Some common carbohydrate architectures found in sea cucumber glycosides.

Triterpene glycosides can be classified as holostane type having 3β -hydroxy- 5α -lanostano- $\gamma(18,20)$ -lactone structural feature and nonholostane type do not have a $\gamma(18,20)$ -lactone but have other structural features like holostane type glycosides.

4.1. Holostane Type Triterpene Glycosides

Depending on the position of double bond in the B and C ring of the aglycone (Figure 1), holostane type glycosides can be further subdivided into three groups: glycosides with 3β -hydroxyholost-7(8)-ene, 3β -hydroxyholost-9(11)-ene, and 3β -hydroxyholost-8(9)-ene aglycone skeletons. There are eight pentacyclic triterpene and 30 alkane side chain aglycone architectures commonly found in holostane type glycosides (Figure 4). In these architectures, certain functional groups are generally attached to the specific carbons: keto and β -acetoxy groups at C-16, and α -hydroxy group at C-12 and C-17.

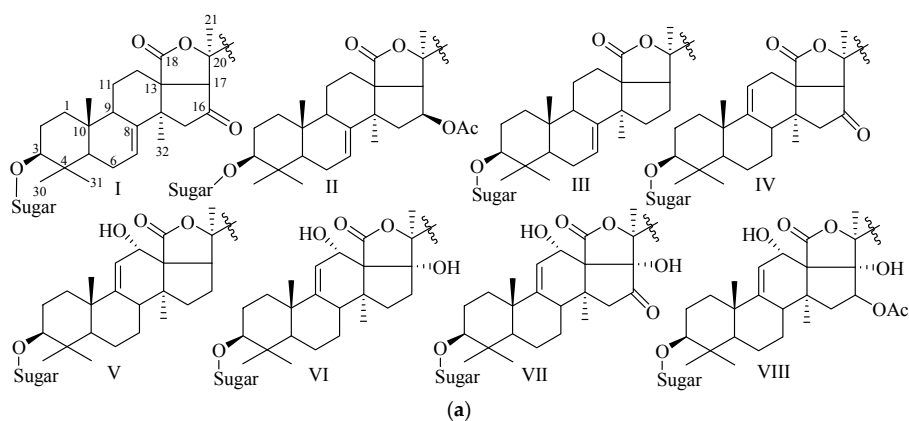


Figure 4. Cont.

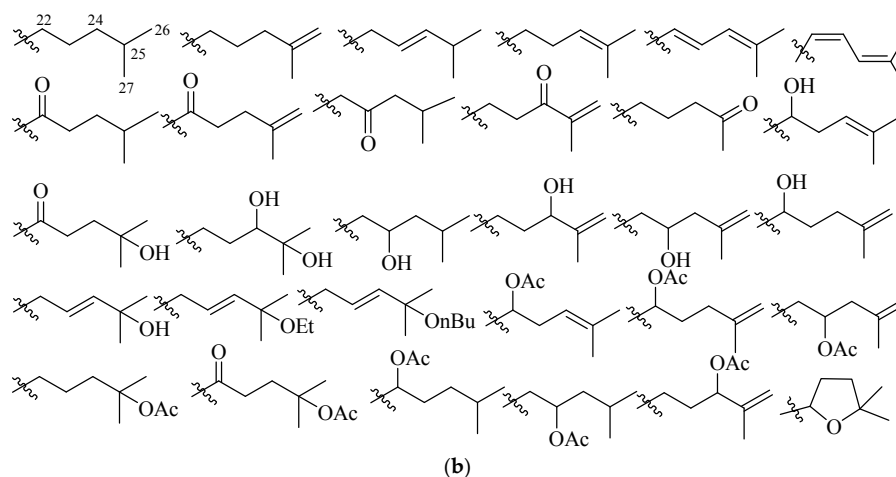


Figure 4. Pentacyclic triterpene and alkane side chain skeletons are commonly found in holostane type glycosides. (a) Pentacyclic triterpene skeletons. Substitution by selective functional groups and unsaturation generally take place in the alkane side chain (2-methylpentane) attached to C-20 of the E-ring of aglycone; (b) Alkane side chain architectures.

4.1.1. 3 β -Hydroxyholost-7(8)-ene Skeleton Containing Holostane Glycosides

Substantial number of triterpene glycosides in this category is produced by sea cucumbers. The species *Eupentacta fraudatrix*, *Holothuria lessoni*, *Bohadschia marmorata*, *Stichopus chloronotus* and *Staurocucumis liouvillei* produce most of the compounds in this group. For convenience, the large number of compounds in this category can be further subdivided into four groups depending on the number of sugar units.

Holostane Glycosides with 3 β -Hydroxyholost-7(8)-ene Skeleton and Six Sugar Units

The name of the compounds in this group, their producing species, chemical structures and references are summarized in Table 1 and Figure 5. The most common features of glycosides in this category are the presence of α -acetoxy group at C-23, double bond at C-25(C-26) and terminal 3-O-methyl-D-glucose in carbohydrate chain. An interesting point to be noted in here is that the sulfate group is totally absent in this group of compounds.

Table 1. Name and producing species of glycosides with 3 β -hydroxyholost-7(8)-ene and six sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|------------------------------------|------------------------------|-----------|------------------------------------|----------------------------|-----------|
| Stichoposide C (1) | <i>Thelenota anax</i> | [17] | Stichoposide D (2) | <i>Thelenota anax</i> | [18] |
| Stichoposide E (3) | <i>Stichopus chloronotus</i> | [19] | Stichloroside A ₁ (4) | <i>S. chloronotus</i> | [20] |
| Stichloroside A ₂ (5) | <i>S. chloronotus</i> | [20] | Stichloroside B ₁ (6) | <i>S. chloronotus</i> | [20] |
| Stichloroside B ₂ (7) | <i>S. chloronotus</i> | [20] | Stichloroside C ₁ (8) | <i>S. chloronotus</i> | [20] |
| Stichloroside C ₂ (9) | <i>S. chloronotus</i> | [20] | Synallactoside A ₂ (10) | <i>Synallactes nozawai</i> | [16] |
| Synallactoside B ₁ (11) | <i>S. nozawai</i> | [16] | Variegatuside F (12) | <i>S. variegates</i> | [21] |
| Holotoxin E (13) | <i>S. japonicus</i> | [22] | | | |

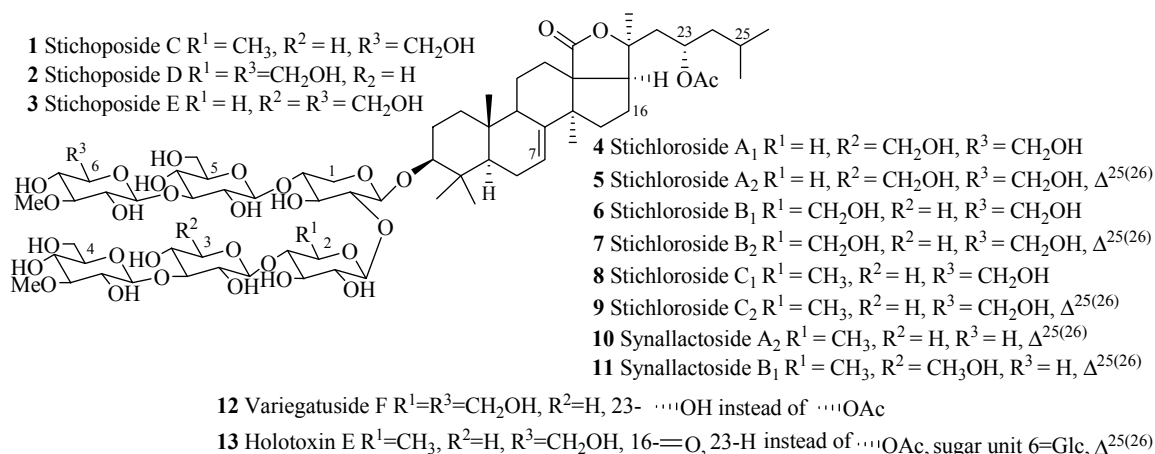


Figure 5. Chemical structures of holostane glycosides with 3β -hydroxyholost-7(8)-ene and six sugar units.

Holostane Glycosides with 3β -Hydroxyholost-7(8)-ene Skeleton and Five Sugar Units

The name of the compounds in this group, their producing species, chemical structures and references are summarized in Table 2 and Figure 6. The most common structural features in this group are the sulfate groups at C-4 of xylose and C-6 of glucose and methylglucose with either β -acetoxy or keto group at C-16 and C-25(26) double bond. A quite number of compounds contain a keto group at C-23. The rare structural features of triterpene glycoside are the presence of 16,22-epoxy group (33), ethoxy group (29) and methylglucuronic acid (51). Cucumarioside A₁-2 (17) is the only example of triterpene glycosides containing an acetate group at C-6 of the terminal sugar unit. Carbohydrate chain can be one branched (14–48 and 52–54) or straight (49–51). 3-O-methyl-D-xylose as a terminal monosaccharide unit that is a characteristic feature of all the glycosides isolated from *Eupentacta fraudatrix*.

Table 2. Name and producing species of glycosides with 3β -hydroxyholost-7(8)-ene and five sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|--------------------------------------|---------------------------|-----------|--------------------------------------|--------------------------|-----------|
| Cucumarioside A ₀ -1 (14) | <i>Cucumaria japonica</i> | [23] | Cucumarioside A ₀ -2 (15) | <i>C. japonica</i> | [23] |
| Cucumarioside A ₀ -3 (16) | <i>C. japonica</i> | [23] | Cucumarioside A ₁ -2 (17) | <i>C. japonica</i> | [24] |
| Cucumarioside A ₂ -2 (18) | <i>C. japonica</i> | [25] | Cucumarioside A ₂ -3 (19) | <i>C. japonica</i> | [24] |
| Cucumarioside A ₂ -4 (20) | <i>C. japonica</i> | [24] | Cucumarioside A ₂ -5 (21) | <i>C. conicospermium</i> | [26] |
| Cucumarioside A ₄ -2 (22) | <i>C. japonica</i> | [24] | Cucumarioside A ₆ -2 (23) | <i>C. japonica</i> | [27] |
| Cucumarioside A ₇ -1 (24) | <i>C. japonica</i> | [28] | Cucumarioside A ₇ -2 (25) | <i>C. japonica</i> | [28] |
| Cucumarioside A ₇ -3 (26) | <i>C. japonica</i> | [28] | Cucumarioside H (27) | <i>E. fraudatrix</i> | [29] |
| Cucumarioside H ₂ (28) | <i>E. fraudatrix</i> | [30] | Cucumarioside H ₄ (29) | <i>E. fraudatrix</i> | [30] |
| Cucumarioside H ₅ (30) | <i>E. fraudatrix</i> | [29] | Cucumarioside H ₆ (31) | <i>E. fraudatrix</i> | [29] |
| Cucumarioside H ₇ (32) | <i>E. fraudatrix</i> | [29] | Cucumarioside H ₈ (33) | <i>E. fraudatrix</i> | [29] |
| Cucumarioside I ₁ (34) | <i>E. fraudatrix</i> | [31] | Cucumarioside I ₂ (35) | <i>E. fraudatrix</i> | [32] |
| Cucumarioside I ₃ (36) | <i>E. fraudatrix</i> | [31] | Frondoside A (37) | <i>C. frondosa</i> | [33] |
| Frondoside B (38) | <i>C. frondosa</i> | [34] | Frondoside A ₂ -1 (39) | <i>C. frondosa</i> | [35] |
| Frondoside A ₂ -2 (40) | <i>C. frondosa</i> | [35] | Frondoside A ₂ -3 (41) | <i>C. frondosa</i> | [35] |
| Frondoside A ₂ -4 (42) | <i>C. frondosa</i> | [36] | Calcigeroside C ₂ (43) | <i>P. calcigera</i> | [37] |
| Calcigeroside D ₂ (44) | <i>P. calcigera</i> | [38] | Calcigeroside E (45) | <i>P. calcigera</i> | [38] |
| Colochiroside A (46) | <i>C. anceps</i> | [39] | Cucumarioside C ₁ (47) | <i>E. fraudatrix</i> | [40] |
| Cucumarioside C ₂ (48) | <i>E. fraudatrix</i> | [40] | Synallactoside B ₂ (49) | <i>S. nozawai</i> | [16] |
| Synallactoside C (50) | <i>S. nozawai</i> | [16] | Synaptoside A (51) | <i>Synapta maculata</i> | [41] |
| Okhotoside A ₂ -1 (52) | <i>C. okhotensis</i> | [42] | Frondoside A ₇ -1 (53) | <i>C. frondosa</i> | [43] |
| Frondoside A ₇ -2 (54) | <i>C. frondosa</i> | [43] | | | |

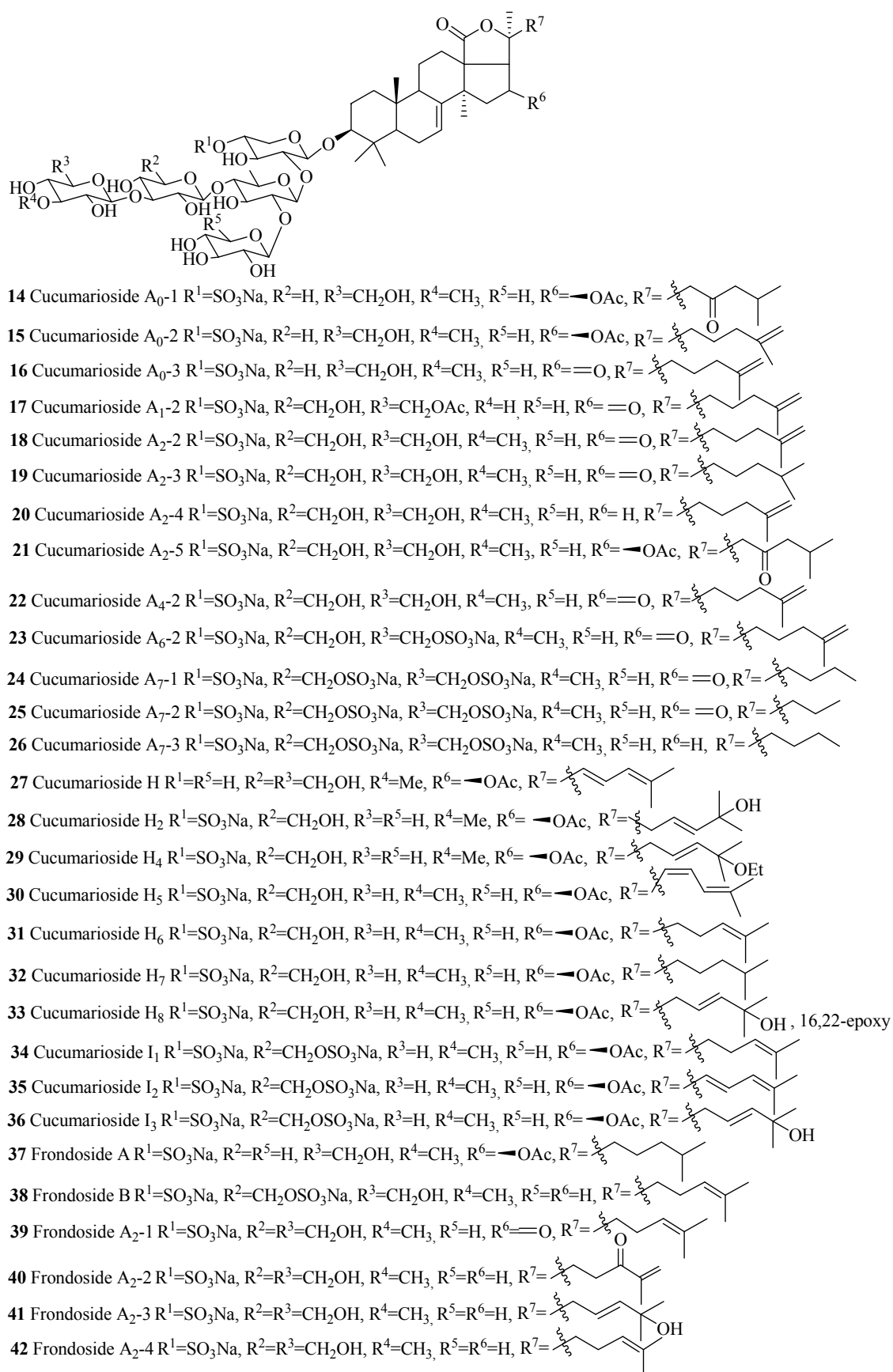


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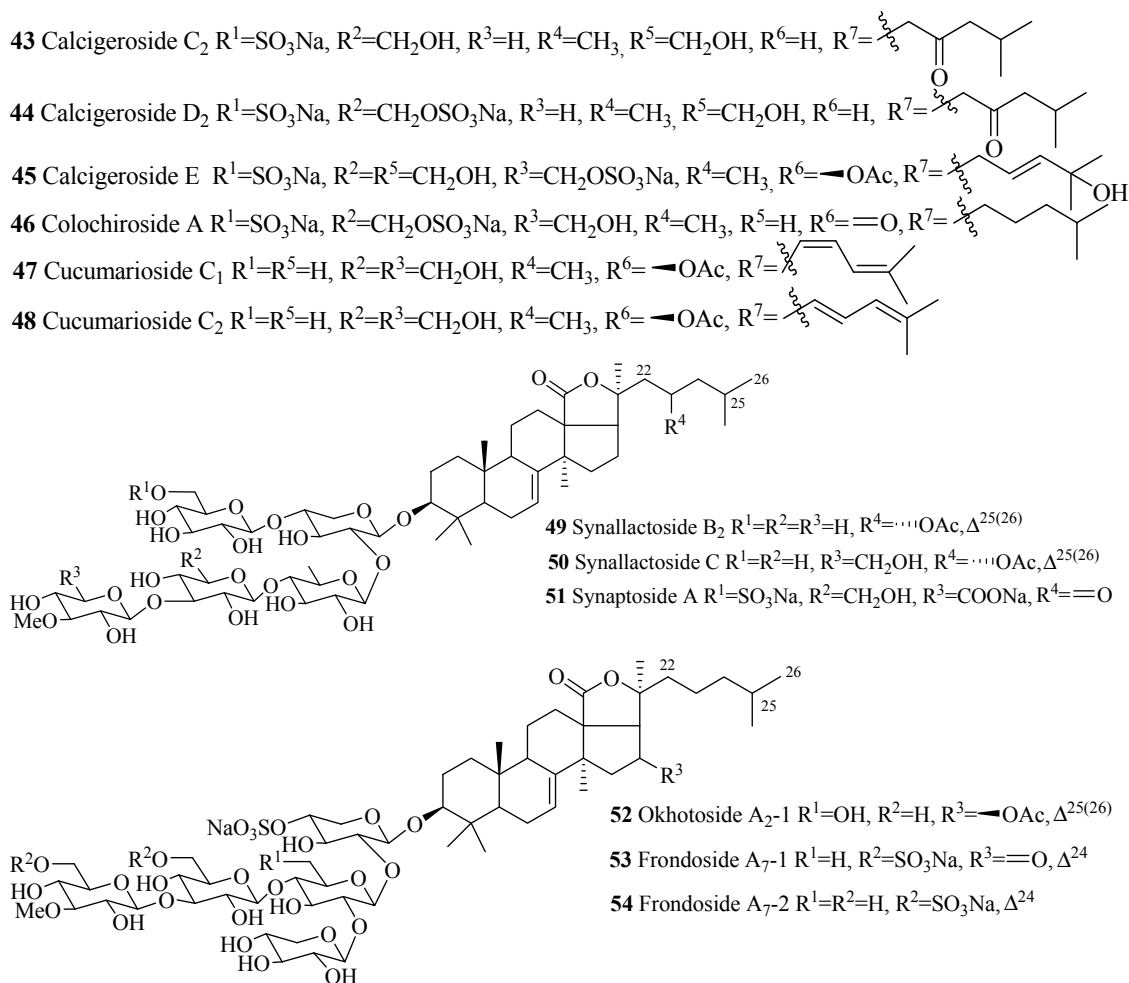


Figure 6. Chemical structures of holostane glycosides with 3β-hydroxyholost-7(8)-ene and five sugar units.

Holostane Glycosides with 3β-Hydroxyholost-7(8)-ene Skeleton and Four Sugar Units

Several compounds in this group were isolated from the species of *Staurocucumis liouvillei* and *Eupentacta fraudatrix* (Table 3). The most common characteristic of glycosides in the group is the presence of sulfate at C-4 of xylose and either keto or β-acetoxy group at C-16 (Figure 7). Some of the compounds in this series, especially liouvillosides, violaceusosides and cucumechinosides, may contain up to three sulfates in their carbohydrate chain. The presence of α-hydroxy at C-12 and C-17 (78 and 79), artifact *n*-butoxy (113) and ethoxy (114) groups at C-25, and three consecutive xylose sugar units in carbohydrate chain (72) are rare structural features in this category. Cucumariosides A₁ (111), A₅ (115) and A₁₁ (118) are the desulfated derivatives of cucumariosides G₁ (123), G₃ (124) and G₄ (125), respectively.

Table 3. Name and producing species of glycosides with 3β-hydroxyholost-7(8)-ene and four sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|-----------------------------------|---------------------------------|-----------|-----------------------------------|----------------------|-----------|
| Liouvilloside A (55) | <i>Staurocucumis liouvillei</i> | [44] | Liouvilloside A ₁ (56) | <i>S. liouvillei</i> | [45] |
| Liouvilloside A ₂ (57) | <i>S. liouvillei</i> | [45] | Liouvilloside A ₃ (58) | <i>S. liouvillei</i> | [45] |
| Liouvilloside A ₅ (59) | <i>S. liouvillei</i> | [46] | Liouvilloside B (60) | <i>S. liouvillei</i> | [44] |
| Liouvilloside B ₁ (61) | <i>S. liouvillei</i> | [45] | Liouvilloside B ₂ (62) | <i>S. liouvillei</i> | [45] |
| Violaceuside A (63) | <i>P. violaceus</i> | [47] | Violaceuside B (64) | <i>P. violaceus</i> | [47] |
| Violaceuside I (65) | <i>P. violaceus</i> | [48] | Violaceuside II (66) | <i>P. violaceus</i> | [48] |

Table 3. Cont.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|-------------------------------------|---------------------------------|-----------|-------------------------------------|--------------------------|-----------|
| Violaceuside III (67) | <i>P. violeceus</i> | [48] | Intercedenside A (68) | <i>M. intercedens</i> | [49] |
| Intercedenside B (67) | <i>Mensamria intercedens</i> | [49] | Intercedenside C (70) | <i>M. intercedens</i> | [49] |
| Intercedenside D (71) | <i>M. intercedens</i> | [50] | Intercedenside E (72) | <i>M. intercedens</i> | [50] |
| Intercedenside F (73) | <i>M. intercedens</i> | [50] | Intercedenside G (74) | <i>M. intercedens</i> | [50] |
| Intercedenside H (75) | <i>M. intercedens</i> | [50] | Intercedenside I (76) | <i>M. intercedens</i> | [50] |
| Patagonicoside A (77) | <i>Psolus patagonicus</i> | [51] | Patagonicoside B (78) | <i>P. patagonicus</i> | [52] |
| Patagonicoside C (79) | <i>P. patagonicus</i> | [52] | Philinopside A (80) | <i>P. quadrangularis</i> | [53] |
| Philinopside B (81) | <i>Pentacta quadrangularis</i> | [53] | Philinopside E (82) | <i>P. quadrangularis</i> | [54] |
| Philinopside F (83) | <i>P. quadrangularis</i> | [54] | Mollisoside A (84) | <i>A. mollis</i> | [55] |
| Mollisoside B ₂ (85) | <i>Australostichopus mollis</i> | [55] | Eximisoside A (86) | <i>P. eximius</i> | [56] |
| Pseudostichoposide A (87) | <i>Pseudostichopus trachus</i> | [57] | Cucumarioside F ₁ (88) | <i>E. fraudatrix</i> | [58] |
| Cucumarioside F ₂ (89) | <i>E. fraudatrix</i> | [58] | Pseudocnoside A (90) | <i>P. leoninus</i> | [59] |
| Typicoside A ₁ (91) | <i>Actinocucumis typica</i> | [60] | Typicoside A ₂ (92) | <i>A. typica</i> | [60] |
| Typicoside B ₁ (93) | <i>A. typica</i> | [60] | Typicoside C ₁ (94) | <i>A. typica</i> | [60] |
| Typicoside C ₂ (95) | <i>A. typica</i> | [60] | Frondoside A ₁ (96) | <i>C. okhotensis</i> | [61] |
| Okhotoside A ₁ -1 (97) | <i>Cucumaria okhotensis</i> | [61] | Okhotoside B ₁ (98) | <i>C. okhotensis</i> | [62] |
| Okhotoside B ₂ (99) | <i>C. okhotensis</i> | [62] | Okhotoside B ₃ (100) | <i>C. okhotensis</i> | [62] |
| Colochiroside A ₁ (101) | <i>Colochirus robustus</i> | [63] | Colochiroside A ₂ (102) | <i>C. robustus</i> | [63] |
| Colochiroside A ₃ (103) | <i>C. robustus</i> | [63] | Colochiroside B ₁ (104) | <i>C. robustus</i> | [64] |
| Colochiroside B ₂ (105) | <i>C. robustus</i> | [64] | Colochiroside B ₃ (106) | <i>C. robustus</i> | [64] |
| Violaceosides C (107) | <i>P. violaceus</i> | [65] | Violaceosides D (108) | <i>P. violaceus</i> | [65] |
| Violaceosides E (109) | <i>P. violaceus</i> | [65] | Violaceosides G (110) | <i>P. violaceus</i> | [65] |
| Cucumarioside A ₁ (111) | <i>E. fraudatrix</i> | [66] | Cucumarioside A ₂ (112) | <i>E. fraudatrix</i> | [67] |
| Cucumarioside A ₃ (113) | <i>E. fraudatrix</i> | [66] | Cucumarioside A ₄ (114) | <i>E. fraudatrix</i> | [66] |
| Cucumarioside A ₅ (115) | <i>E. fraudatrix</i> | [66] | Cucumarioside A ₆ (116) | <i>E. fraudatrix</i> | [66] |
| Cucumarioside A ₇ (117) | <i>E. fraudatrix</i> | [67] | Cucumarioside A ₁₁ (118) | <i>E. fraudatrix</i> | [67] |
| Cucumarioside A ₁₂ (119) | <i>E. fraudatrix</i> | [66] | Cucumarioside A ₁₃ (120) | <i>E. fraudatrix</i> | [67] |
| Cucumarioside A ₁₄ (121) | <i>E. fraudatrix</i> | [67] | Cucumarioside A ₁₅ (122) | <i>E. fraudatrix</i> | [66] |
| Cucumarioside G ₁ (123) | <i>C. fraudatrix</i> | [68] | Cucumarioside G ₃ (124) | <i>E. fraudatrix</i> | [69] |
| Cucumarioside G ₄ (125) | <i>E. fraudatrix</i> | [70] | Pentactaside B (126) | <i>P. quadrangularis</i> | [71] |
| Pentactaside C (127) | <i>P. quadrangularis</i> | [71] | Pseudostichoposide B (128) | <i>P. trachus</i> | [72] |
| Variegatuside A (129) | <i>S. variegates</i> | [73] | Variegatuside C (130) | <i>S. variegates</i> | [21] |
| Synallactoside A ₁ (131) | <i>S. nozawai</i> | [16] | Thelenotoside A (132) | <i>Thelenota ananas</i> | [74] |
| Thelenotoside B (133) | <i>T. ananas</i> | [74] | Cucumechinoside A (134) | <i>C. echinata</i> | [75] |
| Cucumechinoside B (135) | <i>C. echinata</i> | [75] | Cucumechinoside C (136) | <i>C. echinata</i> | [75] |
| Cucumechinoside D (137) | <i>C. echinata</i> | [75] | Cucumechinoside E (138) | <i>C. echinata</i> | [75] |
| Cucumechinoside F (139) | <i>C. echinata</i> | [75] | Lefevreoside A ₁ (140) | <i>C. lefevrei</i> | [76] |
| Lefevreoside A ₂ (141) | <i>C. lefevrei</i> | [76] | Lefevreoside C (142) | <i>C. lefevrei</i> | [76] |
| Lefevreoside D (143) | <i>C. lefevrei</i> | [76] | | | |

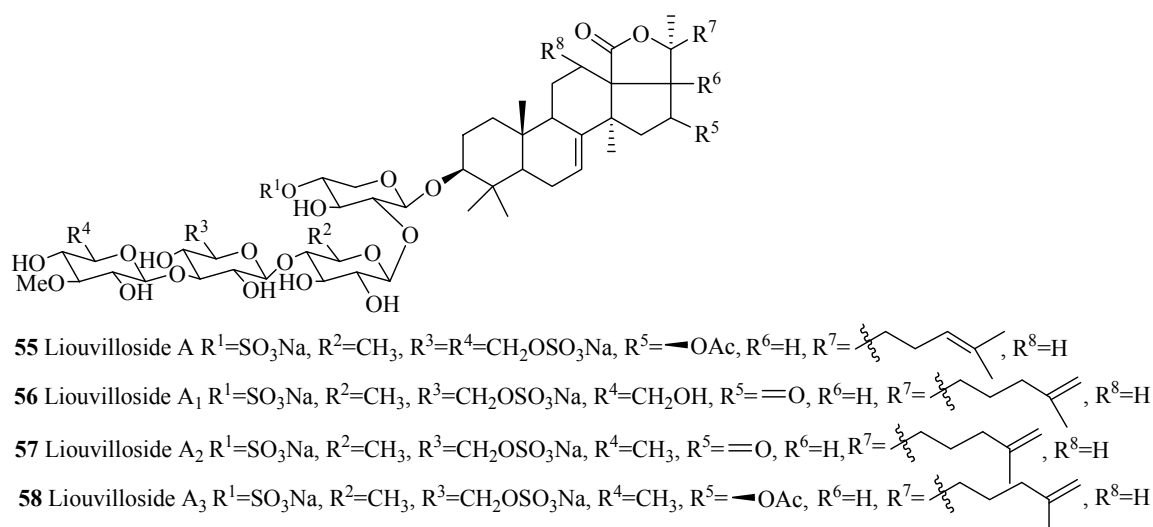


Figure 7. Cont.

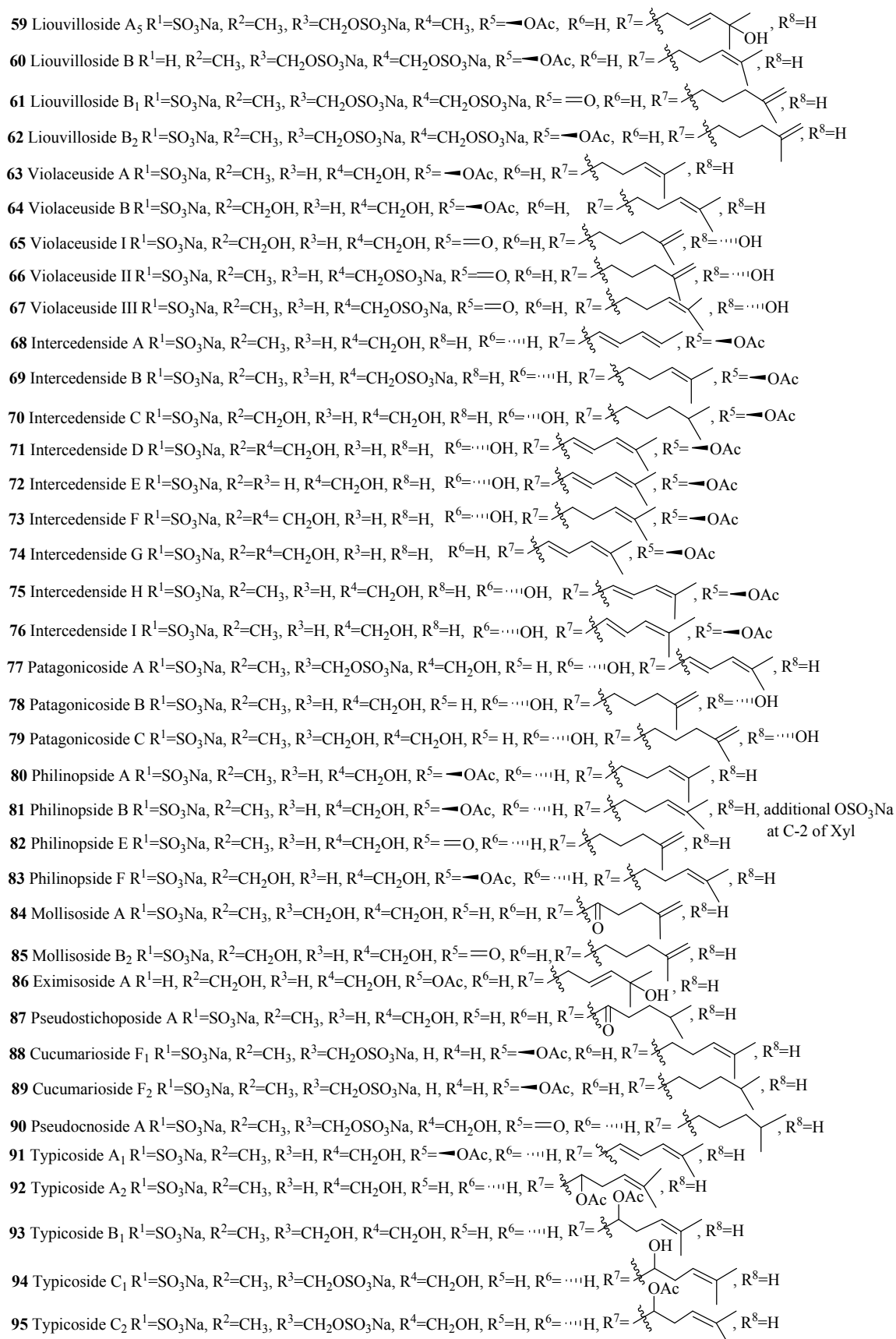


Figure 7. Cont.

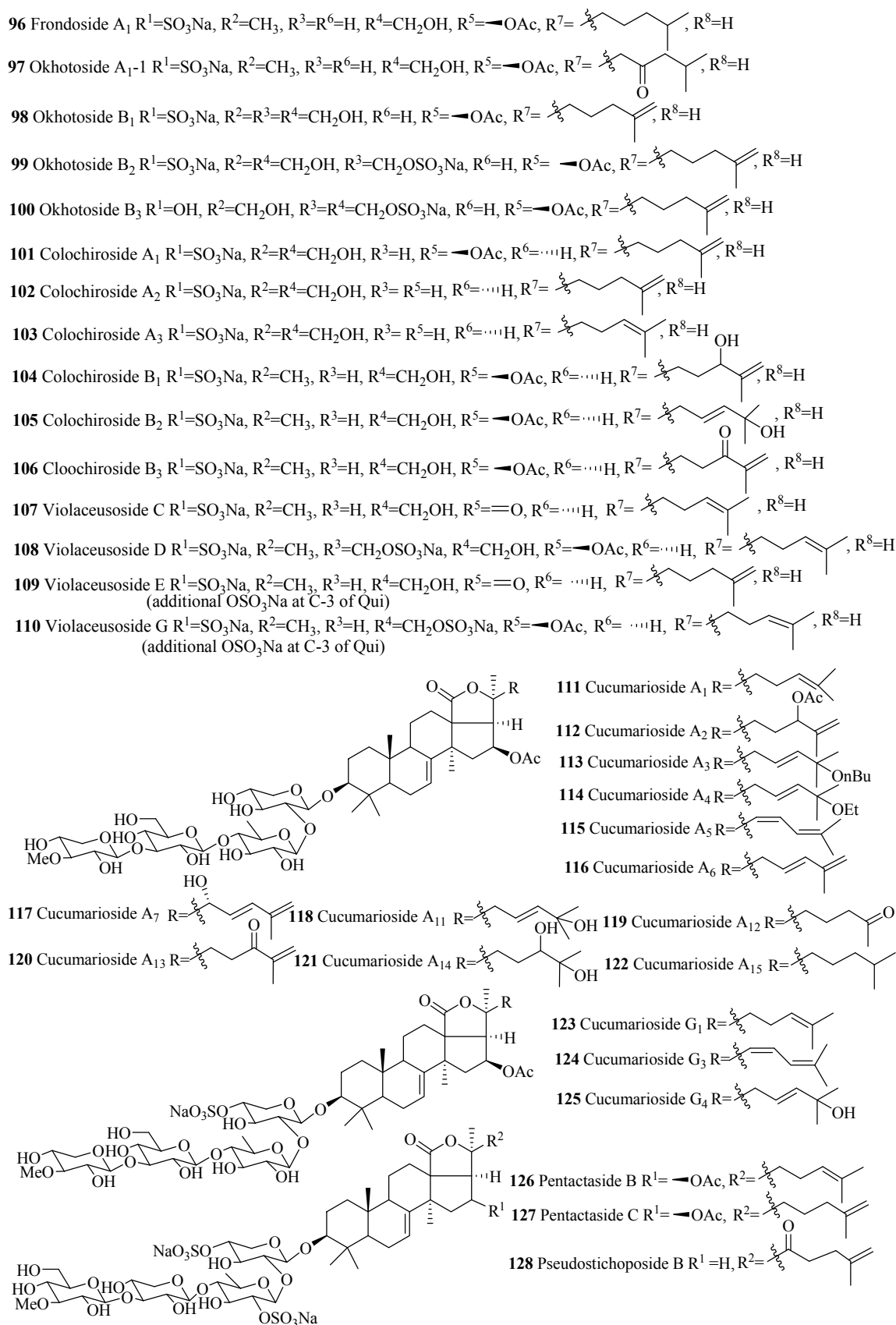


Figure 7. Cont.

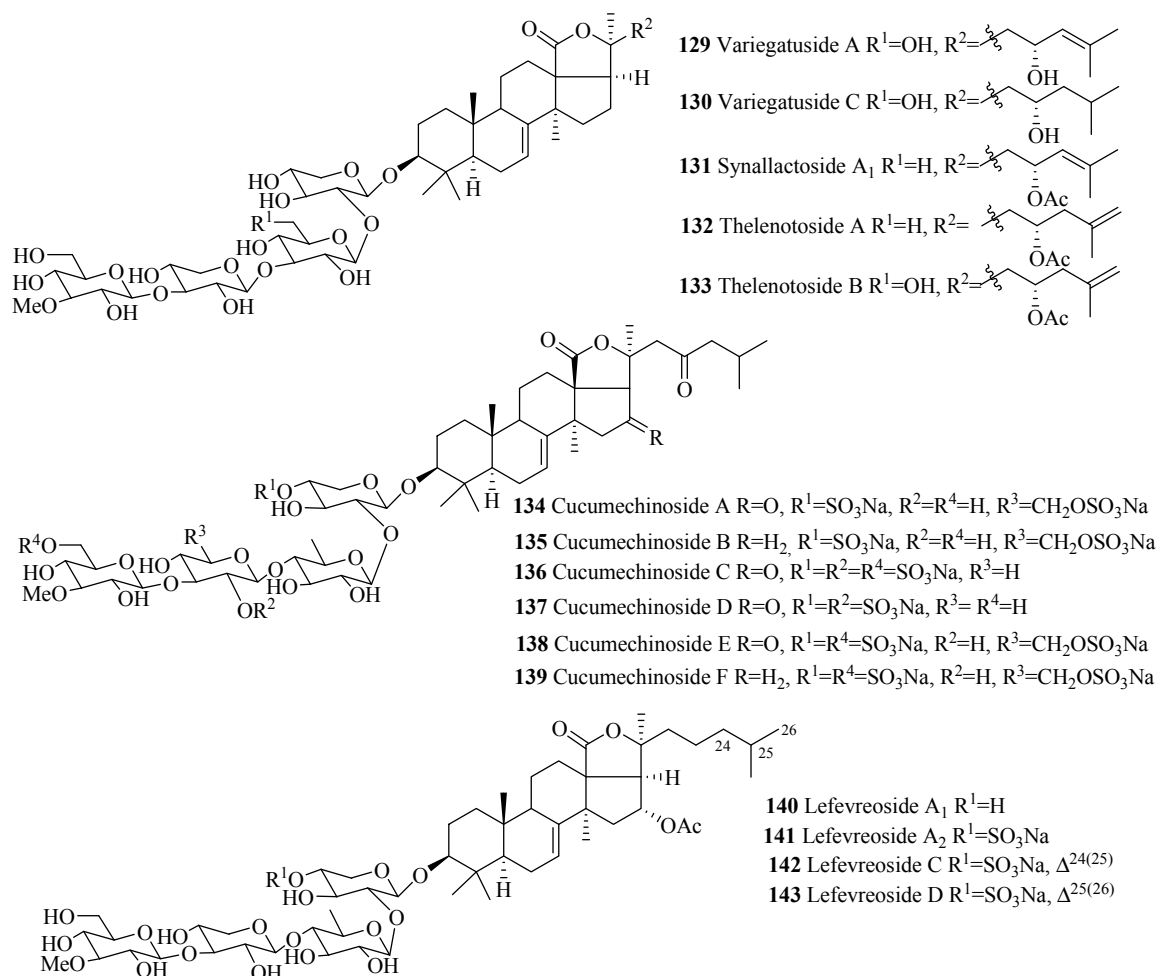


Figure 7. Chemical structures of holostane glycosides with 3 β -hydroxyholost-7(8)-ene and four sugar units.

Holostane Glycosides with 3 β -Hydroxyholost-7(8)-ene Skeleton and 1–3 Sugar Units

The name of the compounds in this group, their producing species, chemical structures and references are summarized in Table 4 and Figure 8. The most common feature of triterpene glycosides is the presence of double bond at C-25(26). Cucumarioside B₁ (146) is the geometric isomer of cucumarioside B₂ (142) and pentactaside III (148) is the positional isomer of stichoposide A (153).

Table 4. Name and producing species of glycosides with 3 β -hydroxyholost-7(8)-ene and 1–3 sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|------------------------------------|--------------------------------|-----------|------------------------------------|--------------------------|-----------|
| Pentactaside I (144) | <i>Pentacta quadrangularis</i> | [77] | Pentactaside II (145) | <i>P. quadrangularis</i> | [77] |
| Cucumarioside B ₁ (146) | <i>E. fraudatrix</i> | [78] | Cucumarioside B ₂ (147) | <i>E. fraudatrix</i> | [78] |
| Pentactaside III (148) | <i>P. quadrangularis</i> | [77] | Stichoposide A (149) | <i>S. cloronotus</i> | [79] |
| Stichoposide B (150) | <i>Stichopus cloronotus</i> | [79] | Stichorrenoside A (151) | <i>Stichopus horrens</i> | [80] |
| Stichorrenoside B (152) | <i>S. horrens</i> | [80] | Stichorrenoside C (153) | <i>S. horrens</i> | [80] |
| Stichorrenoside D (154) | <i>S. horrens</i> | [80] | Hillaside A (155) | <i>H. hilla</i> | [81] |

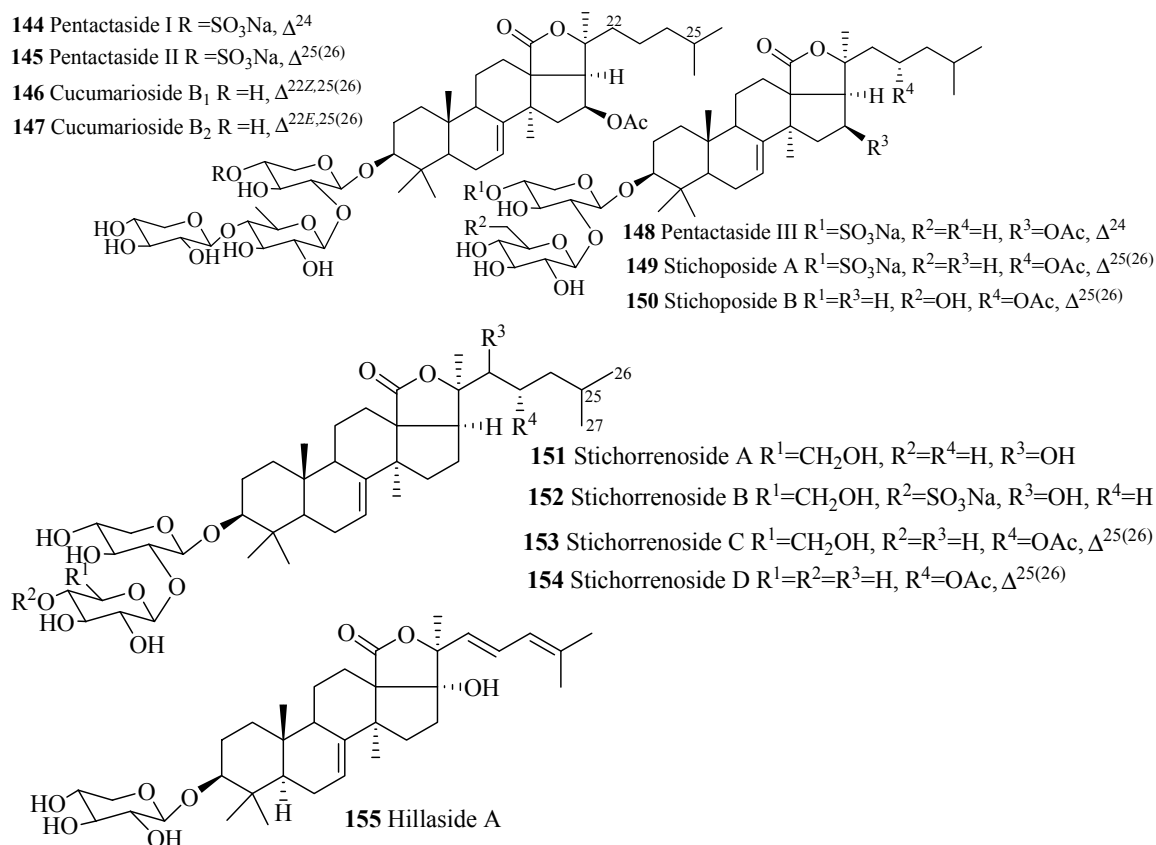


Figure 8. Chemical structures of holostane glycosides with 3β-hydroxyholost-7(8)-ene and 1–3 sugar units.

4.1.2. 3β-Hydroxyholost-9(11)-ene Skeleton Containing Holostane Glycosides

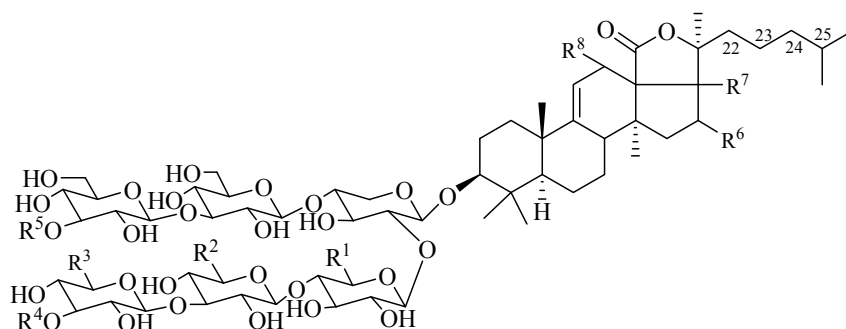
The species *Holothuria lessoni*, *Bohadschia marmorata* and *Bohadschia bivittata* produce most of the compounds in this group. For convenience, the large number of compounds in this category can also be further subdivided into four groups depending on the number of sugar units

Holostane Glycosides with 3β-Hydroxyholost-9(11)-ene Skeleton and Six Sugar Units

Similar to 3β-hydroxyholost-7(8)-ene skeleton with six sugar units (Figure 5), 3β-hydroxyholost-9(11)-ene skeleton with six sugar units glycosides also do not have any sulfate group in their carbohydrate chain (Figure 9 and Table 5) except cladolosides K₁, K₂ and L₁ (197–199). The most common structural feature of triterpene glycosides in this category is the presence of 3-*O*-methyl-*D*-glucose at the both end of the straight carbohydrate chain. Holotoxin and parvimoside series (156–166) of compounds have a keto group at position C-16. Double bond at C-25(26) among holotoxins (156–163) is common, except 26-nor-25-oxo-holotoxin A₁ (159), where the double bond is replaced by a keto group. The α-hydroxy groups at C-12 and C-17 are commonly found in the aglycone part of lessonioside series of glycosides (175–177). The α-hydroxy group at C-12 and C-17, and 22,25-epoxy are common structural characteristics of holothurinosides (183–188). Acetoxy group at C-16 and C-22 are frequently observed in cladoloside glycosides (189–199).

Table 5. Name and producing species of glycosides with 3 β -hydroxyholost-9(11)-ene and six sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Pro. Species | Reference |
|---|-------------------------------|-----------|--------------------------------------|-----------------------|-----------|
| Holotoxin A (156) | <i>Stichopus japonicus</i> | [82] | Holotoxin A ₁ (157) | <i>S. japonicus</i> | [22] |
| 25,26-dihydroxyholotoxin A ₁ (158) | <i>Apostichopus japonicus</i> | [83] | Oxo-holotoxin A ₁ (159) | <i>A. japonicus</i> | [22] |
| Holotoxin B (160) | <i>S. japonicus</i> | [22] | Holotoxin B ₁ (161) | <i>S. japonicus</i> | [22] |
| Holotoxin D (162) | <i>S. japonicus</i> | [22] | Holotoxin D ₁ (163) | <i>A. japonicus</i> | [83] |
| Parvimoside A (164) | <i>Stichopus parvimensis</i> | [84] | Parvimoside B (165) | <i>S. parvimensis</i> | [84] |
| Bivittoside C (166) | <i>Bohadschia biviittata</i> | [85] | Bivittoside D (167) | <i>B. biviittata</i> | [85] |
| 25-acetoxybivittoside D (168) | <i>Bohadschia marmorata</i> | [86] | Arguside B (169) | <i>B. argus</i> | [87] |
| Arguside C (170) | <i>B. argus</i> | [87] | Marmoratoside A (171) | <i>B. marmorata</i> | [86] |
| Marmoratoside B (172) | <i>B. marmorata</i> | [86] | Impatienside A (173) | <i>H. impatiens</i> | [86] |
| 17 α -hydroxyimpatienside A (174) | <i>B. marmorata</i> | [86] | Lessonioside A (175) | <i>H. lessoni</i> | [88] |
| Lessonioside B (176) | <i>Holothuria lessoni</i> | [88] | Lessonioside D (177) | <i>H. lessoni</i> | [88] |
| Variegatuside E (178) | <i>S. variegates</i> | [21] | Lessonioside C (179) | <i>H. lessoni</i> | [88] |
| Lessonioside E (180) | <i>Holothuria lessoni</i> | [88] | Lessonioside F (181) | <i>H. lessoni</i> | [88] |
| Lessonioside G (182) | <i>H. lessoni</i> | [88] | Holothurinoside F (183) | <i>B. subrubra</i> | [89] |
| Holothurinoside H (184) | <i>B. subrubra</i> | [89] | Holothurinoside H ₁ (185) | <i>B. subrubra</i> | [89] |
| Holothurinoside I (186) | <i>B. subrubra</i> | [89] | Holothurinoside I ₁ (187) | <i>B. subrubra</i> | [89] |
| Holothurinoside K ₁ (188) | <i>B. subrubra</i> | [89] | Cladoloside C (189) | <i>C. schmeltzii</i> | [90] |
| Cladoloside C ₁ (190) | <i>Cladolabes schmeltzii</i> | [90] | Cladoloside C ₂ (191) | <i>C. schmeltzii</i> | [90] |
| Cladoloside C ₃ (192) | <i>C. schmeltzii</i> | [91] | Cladoloside D (193) | <i>C. schmeltzii</i> | [90] |
| Cladoloside G (194) | <i>C. schmeltzii</i> | [91] | Cladoloside H ₁ (195) | <i>C. schmeltzii</i> | [91] |
| Cladoloside H ₂ (196) | <i>C. schmeltzii</i> | [91] | Cladoloside K ₁ (197) | <i>C. schmeltzii</i> | [92] |
| Cladoloside K ₂ (198) | <i>C. schmeltzii</i> | [92] | Cladoloside L ₁ (199) | <i>C. schmeltzii</i> | [92] |



156 Holotoxin A $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=O$, $R^7=H$, $R^8=H$, $\Delta^{25(26)}$

157 Holotoxin A₁ $R^1=R^4=R^5=CH_3$, $R^2=H$, $R^3=CH_2OH$, $R^6=O$, $R^7=H$, $R^8=H$, $\Delta^{25(26)}$

158 25,26-dihydroxyholotoxin A₁ $R^1=R^4=R^5=CH_3$, $R^2=R^7=R^8=H$, $R^3=CH_2OH$, $R^6=O$, 25-OH, 26-OH

159 26-nor-25-oxo-holotoxin A₁ $R^1=R^2=R^4=R^5=CH_3$, $R^3=CH_2OH$, $R^6=O$, $R^7=H$, $R^8=H$, 25=O

160 Holotoxin B $R^1=R^4=CH_3$, $R^2=R^3=CH_2OH$, $R^5=H$, $R^6=O$, $R^7=H$, $R^8=H$, $\Delta^{25(26)}$

161 Holotoxin B₁ $R^1=R^4=CH_3$, $R^2=R^5=H$, $R^3=CH_2OH$, $R^6=O$, $R^7=H$, $R^8=H$, $\Delta^{25(26)}$

162 Holotoxin D $R^1=R^3=CH_2OH$, $R^2=H$, $R^4=R^5=CH_3$, $R^6=O$, $R^7=H$, $R^8=H$, $\Delta^{25(26)}$

163 Holotoxin D₁ $R^1=R^3=CH_2OH$, $R^2=R^5=R^7=R^8=H$, $R^4=CH_3$, $R^6=O$, $\Delta^{25(26)}$

164 Parvimoside A $R^1=R^4=CH_3$, $R^2=R^3=CH_2OH$, $R^5=H$, $R^6=O$, $R^7=H$, $R^8=H$

165 Parvimoside B $R^1=R^4=CH_3$, $R^2=R^5=H$, $R^3=CH_2OH$, $R^6=O$, $R^7=H$, $R^8=H$

166 Bivittoside C $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7=H$, $R^8=H$

Figure 9. Cont.

- 167** Bivittoside D $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7= \cdots H$, $R^8= \cdots OH$
168 25-acetoxy bivittoside D $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7= \cdots H$, $R^8= \cdots OH$, 25-OAc
169 Arguside B $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7= \cdots OH$, $R^8= \cdots OH$
170 Arguside C $R^1= R^2=R^3=CH_2OH$, $R^4=R^5=CH_3$, $R^6=H$, $R^7= \cdots H$, $R^8= \cdots OH$
171 Marmoratoside A $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7=H$, $R^8= \cdots OH$, $\Delta^{25(26)}$
172 Marmoratoside B $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7=H$, $R^8= \cdots OH$, 25-OH, Δ^{23}
173 Impatienside A $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7=H$, $R^8= \cdots OH$, Δ^{24}
174 17 α -hydroxy impatienside A $R^1=R^4=R^5=CH_3$, $R^2=R^3=CH_2OH$, $R^6=H$, $R^7= \cdots OH$, $R^8= \cdots OH$, Δ^{24}
175 Lessonioside A $R^1=R^4=R^5=CH_3$, $R^2=H$, $R^3=CH_2OH$, $R^6=OAc$, $R^7= \cdots OH$, $R^8= \cdots OH$
176 Lessonioside B $R^1=R^3=R^5=CH_3$, $R^2=CH_2OH$, $R^4=H$, $R^6=OAc$, $R^7= \cdots OH$, $R^8= \cdots OH$
177 Lessonioside D $R^1=R^4=R^5=CH_3$, $R^2=CH_2OH$, $R^3=H$, $R^6=OAc$, $R^7= \cdots OH$, $R^8= \cdots OH$
178 Variegatuside E $R^1=R^3=CH_2OH$, $R^2=R^6=R^8=H$, $R^4=R^5=Me$, $R^7= \cdots H$, 23- $\cdots OH$

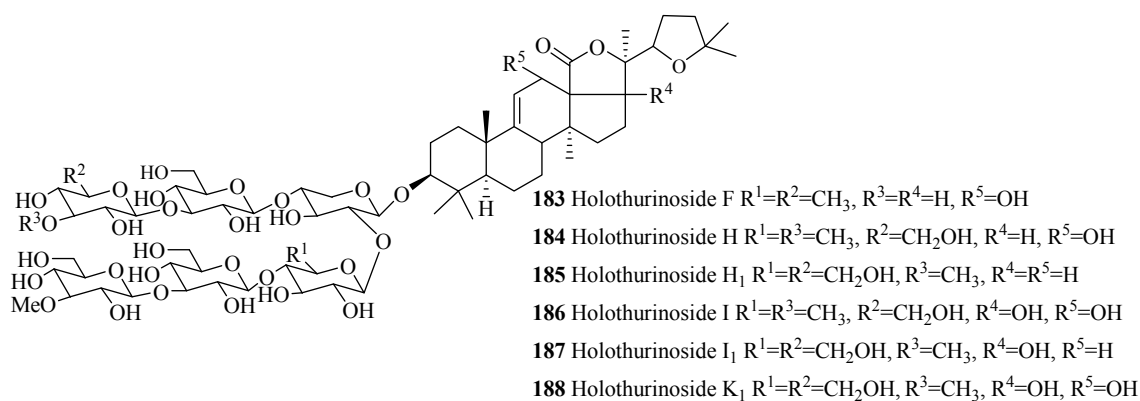
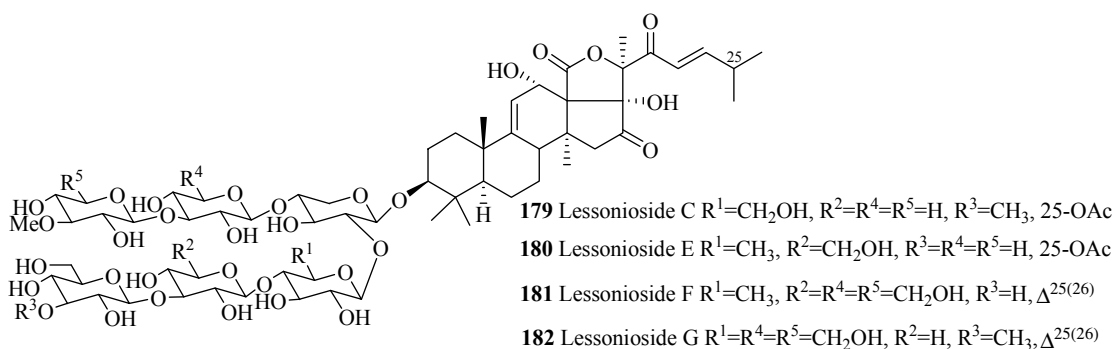


Figure 9. Cont.

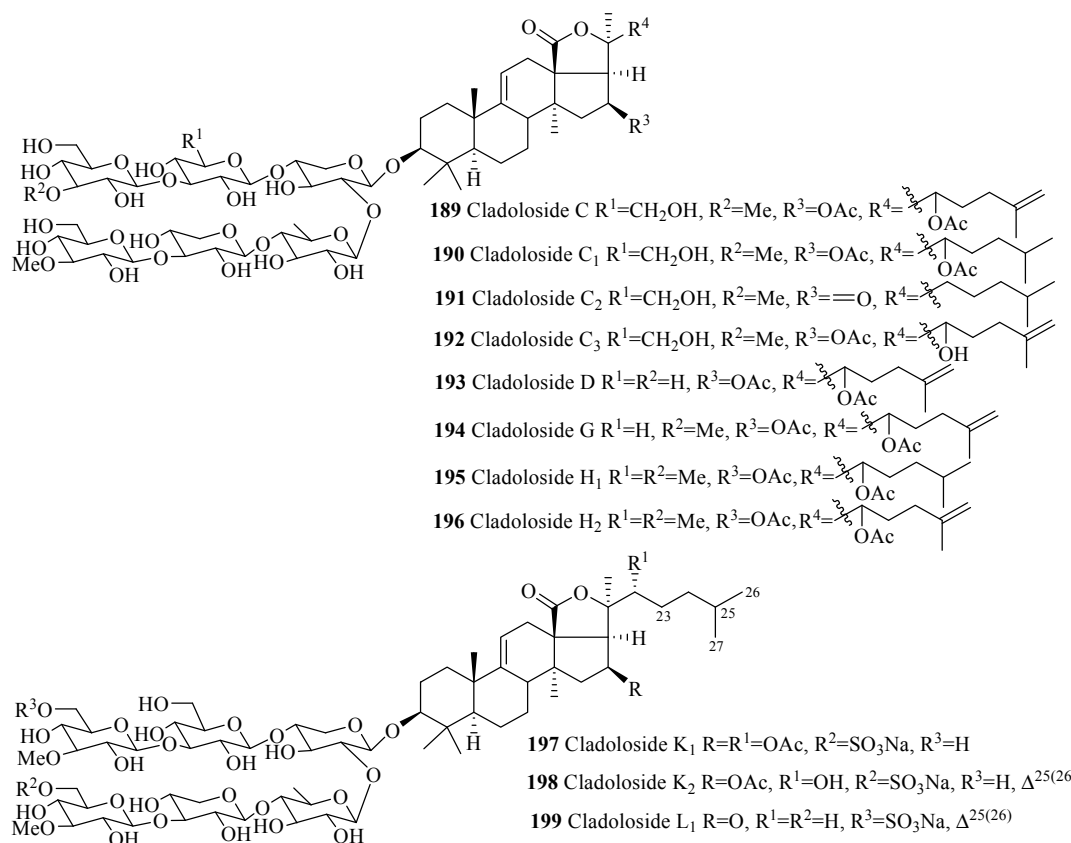


Figure 9. Chemical structures of holostane glycosides with 3 β -hydroxyholost-9(11)-ene and six sugar units.

Holostane Glycosides with 3 β -Hydroxyholost-9(11)-ene Skeleton and Five Sugar Units

The carbohydrate chains of glycosides in this group are either straight (200–218 and 223–229) or branched (219–222) (Figure 10 and Table 6). The 22,25-epoxy (200–202, 213–215) and two acetoxy groups, one at C-16 and another at C-22 (211, 212, 223–228), are common in holothurinosides and cladolosides, respectively. Kolgaosides (204 and 205) and achlioniceosides (216–218) within their own groups have the same carbohydrate chains and the only difference is in their respective aglycone side chains.

Table 6. Name and producing species of glycosides with 3 β -hydroxyholost-9(11)-ene and five sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|--------------------------------------|-----------------------------|-----------|--------------------------------------|--------------------------|-----------|
| Holothurinoside A (200) | <i>Holothuria forskalii</i> | [93] | 17-dehydroxyholothurinoside A (201) | <i>Holothuria grisea</i> | [94] |
| Holothurinoside A ₁ (202) | <i>H. lessoni</i> | [95] | Holothurinoside B (203) | <i>H. forskalii</i> | [93] |
| Kolgaoside A (204) | <i>Kolga hyalina</i> | [96] | Kolgaoside B (205) | <i>K. hyalina</i> | [96] |
| Griseaside A (206) | <i>H. grisea</i> | [94] | Impatienside B (207) | <i>H. axiloga</i> | [97] |
| Arguside F (208) | <i>Holothuria axiloga</i> | [97] | Pervicoside D (209) | <i>H. axiloga</i> | [97] |
| Cladoloside B (210) | <i>A. japonicus</i> | [22] | Cladoloside B ₁ (211) | <i>C. schmeltzii</i> | [90] |
| Cladoloside B ₂ (212) | <i>C. schmeltzii</i> | [90] | Holothurinoside E (213) | <i>H. lessoni</i> | [95] |
| Holothurinoside E ₁ (214) | <i>H. lessoni</i> | [95] | Holothurinoside M (215) | <i>H. lessoni</i> | [95] |
| Achlioniceoside A ₁ (216) | <i>A. violaeuspadata</i> | [98] | Achlioniceoside A ₂ (217) | <i>A. violaeuspadata</i> | [98] |
| Achlioniceoside A ₃ (218) | <i>A. violaeuspadata</i> | [98] | Ds-penaustroside C (219) | <i>P. australis</i> | [99] |
| Ds-penaustroside D (220) | <i>Pentacta australis</i> | [99] | Frondoside A ₂ -6 (221) | <i>C. frondosa</i> | [35] |
| Cladoloside E ₁ (222) | <i>C. schmeltzii</i> | [91] | Cladoloside E ₂ (223) | <i>C. schmeltzii</i> | [91] |
| Cladoloside F ₁ (224) | <i>C. schmeltzii</i> | [91] | Cladoloside F ₂ (225) | <i>C. schmeltzii</i> | [91] |
| Cercodemasoide A (226) | <i>C. anceps</i> | [100] | Cladoloside I ₁ (227) | <i>C. schmeltzii</i> | [92] |
| Cladoloside I ₂ (228) | <i>C. schmeltzii</i> | [92] | Cladoloside J ₁ (229) | <i>C. schmeltzii</i> | [92] |

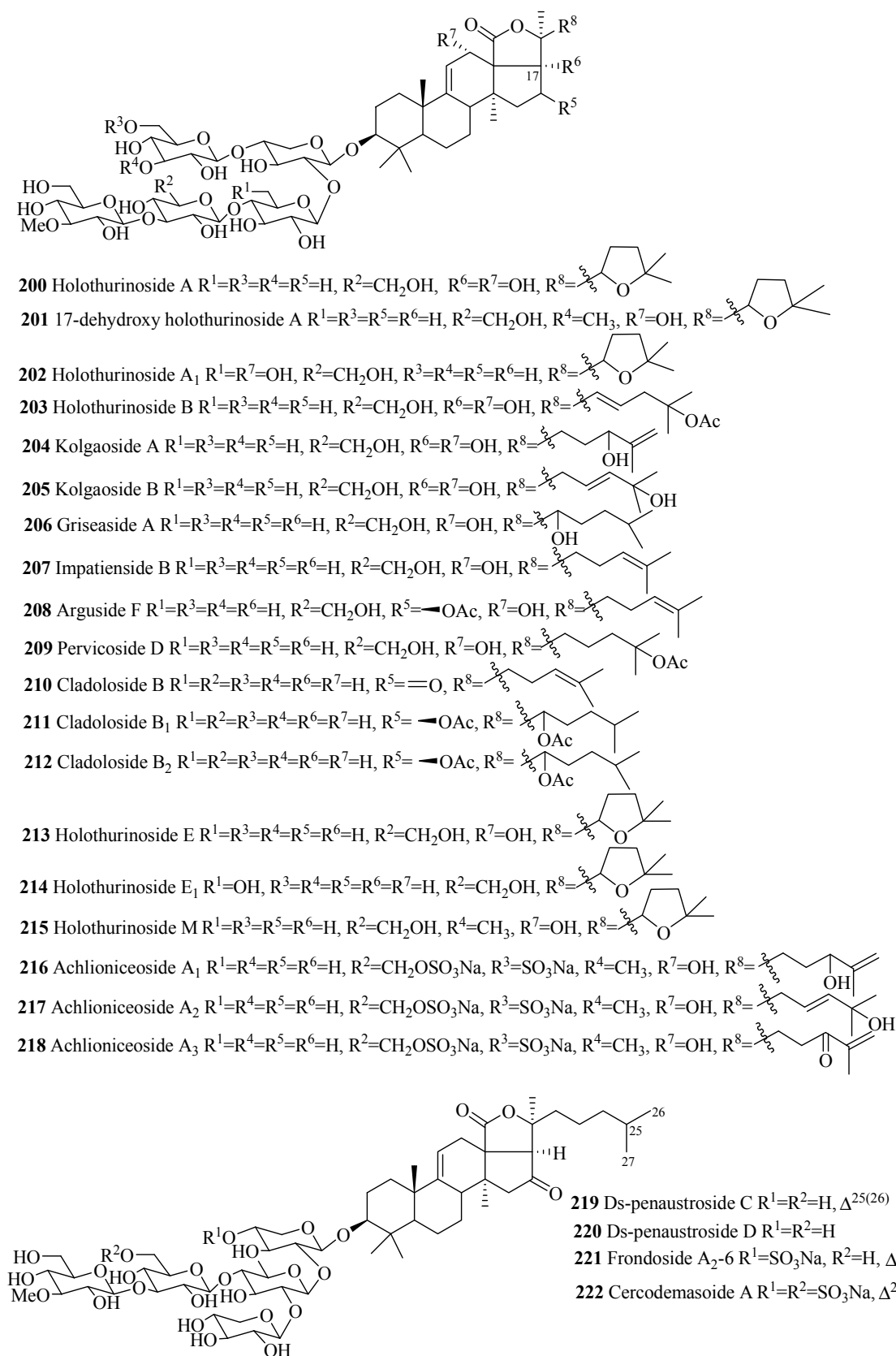


Figure 10. Cont.

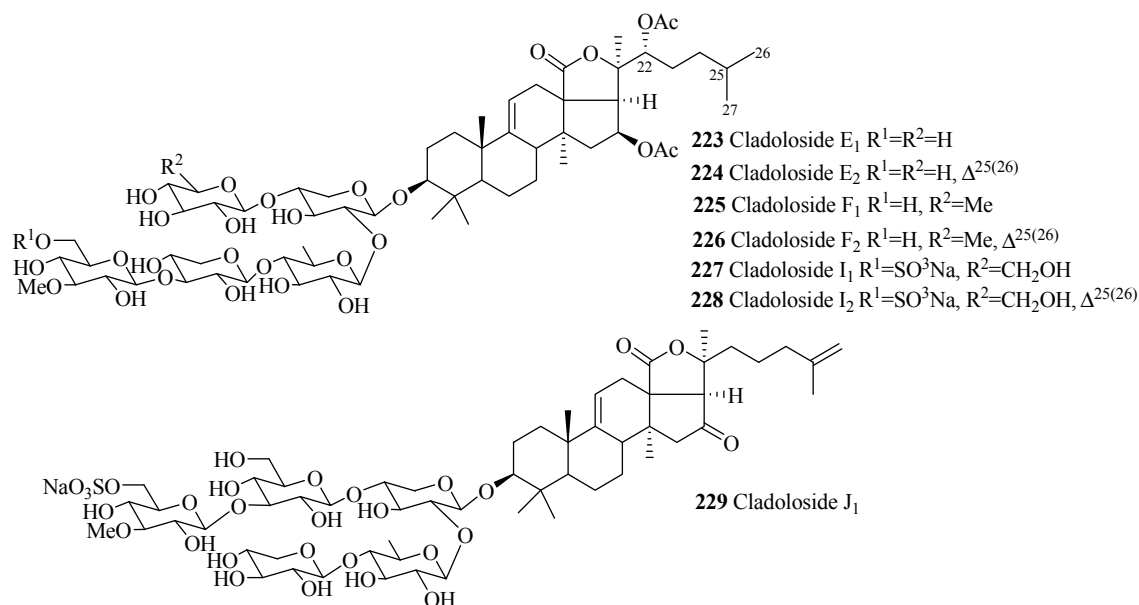


Figure 10. Chemical structures of holostane glycosides with 3β-hydroxyholost-9(11)-ene and five sugar units.

Holostane Glycosides with 3β-Hydroxyholost-9(11)-ene Skeleton and Four Sugar Units

The names and structures of the glycosides belonging to this group are summarized in the Table 7 and Figure 11. Almost all the saponins in this group contain sulfate group at C-4 of xylose sugar. The most common features of holothurins (230–233), scabrasides (235–237) and echinosides (243–249) are the presence of hydroxy groups at C-12 and C-17 (Figure 11). Among the cladoloside series of compounds (266–271), either keto or acetoxy group is commonly found at position C-16 and 22. The uncommon linear sugar chain [3-O-MeGlc (1→3)-Glc (1→4)-Xyl (2→1)-Qui] is observed in bivittoside B (262). Another exceptional feature has been found in this category of compounds is the presence of three consecutive glucose unit in the linear carbohydrate chain (258 and 259).

Table 7. Name and producing species of glycosides with 3β-hydroxyholost-9(11)-ene and four sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|---|-----------------------------|-----------|---|------------------------|-----------|
| Holothurin A (230) | <i>Actinopyga agassizi</i> | [101] | Holothurin A ₁ (231) | <i>H. grisea</i> | [102] |
| Holothurin A ₃ (232) | <i>Holothuria scabra</i> | [103] | Holothurin A ₄ (233) | <i>H. scabra</i> | [103] |
| Holothurinoside C (234) | <i>H. forskalii</i> | [93] | Scabraside A (235) | <i>H. scabra</i> | [104] |
| Scabraside B (236) | <i>H. scabra</i> | [104] | Scabraside D (237) | <i>H. scabra</i> | [105] |
| Fuscocineroside A (238) | <i>H. fuscocinerea</i> | [106] | Fuscocineroside B (239) | <i>H. fuscocinerea</i> | [106] |
| 17-hydroxy fuscocineroside B (240) | <i>B. marmorata</i> | [107] | 25-hydroxy-fuscocineroside B (241) | <i>B. marmorata</i> | [107] |
| Fuscocineroside C (242) | <i>H. fuscocinerea</i> | [106] | Echinoside A (243) | <i>A. echinites</i> | [108] |
| Ds-echinoside A (244) | <i>P. graeffei</i> | [109] | 24-dehydroechinoside A (245) | <i>H. scabra</i> | [105] |
| 22-hydroxy-24-dehydroechinoside A (246) | <i>Actinopyga flammea</i> | [110] | 24-hydroxy-25-dehydroechinoside A (247) | <i>A. flammea</i> | [110] |
| 25-hydroxydehydroechinoside A (248) | <i>A. flammea</i> | [110] | 22-acetoxyechinoside A (249) | <i>A. flammea</i> | [110] |
| Desholothurin A (250) | <i>P. graeffei</i> | [93] | Pervicoside A (251) | <i>H. pervicax</i> | [111] |
| Pervicoside B (252) | <i>H. pervicax</i> | [111] | Pervicoside C (253) | <i>H. pervicax</i> | [111] |
| Arguside A (254) | <i>Bohadschia argus</i> | [112] | Holothurinoside J ₁ (255) | <i>P. graeffei</i> | [95] |
| Hemoiedemside A (256) | <i>H. spectabilis</i> | [113] | Hemoiedemside B (257) | <i>H. spectabilis</i> | [113] |
| Arguside D (258) | <i>B. argus</i> | [114] | Arguside E (259) | <i>B. argus</i> | [114] |
| Psolusoside A (260) | <i>Psolus fabricii</i> | [115] | Liouvilloside A ₄ (261) | <i>S. liouvillei</i> | [46] |
| Bivittoside B (262) | <i>Bohadschia bivitta</i> | [85] | Holothurinoside X (263) | <i>H. lessoni</i> | [116] |
| Holothurinoside Y (264) | <i>H. lessoni</i> | [116] | Holothurinoside Z (265) | <i>H. lessoni</i> | [116] |
| Cladoloside A ₁ (266) | <i>Cladolabes chmeltzii</i> | [117] | Cladoloside A ₂ (267) | <i>C. chmeltzii</i> | [117] |
| Cladoloside A ₃ (268) | <i>C. chmeltzii</i> | [117] | Cladoloside A ₄ (269) | <i>C. chmeltzii</i> | [117] |
| Cladoloside A ₅ (270) | <i>C. chmeltzii</i> | [117] | Cladoloside A ₆ (271) | <i>C. chmeltzii</i> | [117] |
| Colochiroside C (272) | <i>C. chmeltzii</i> | [64] | Colochiroside D (273) | <i>C. robustus</i> | [63] |
| Mollisoside B ₁ (274) | <i>A. mollis</i> | [55] | Neothyonidoside (275) | <i>A. mollis</i> | [118] |

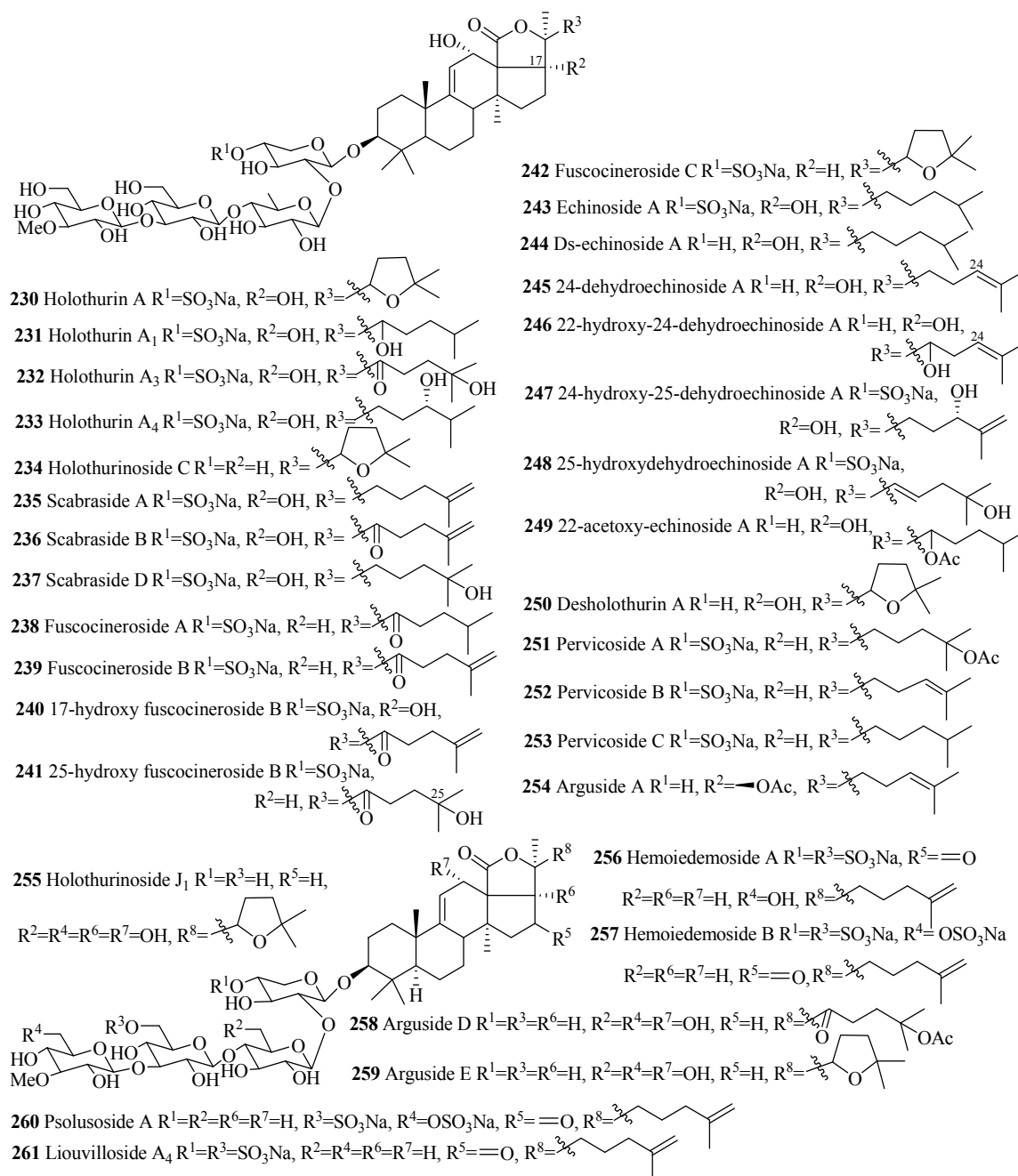


Figure 11. Cont.

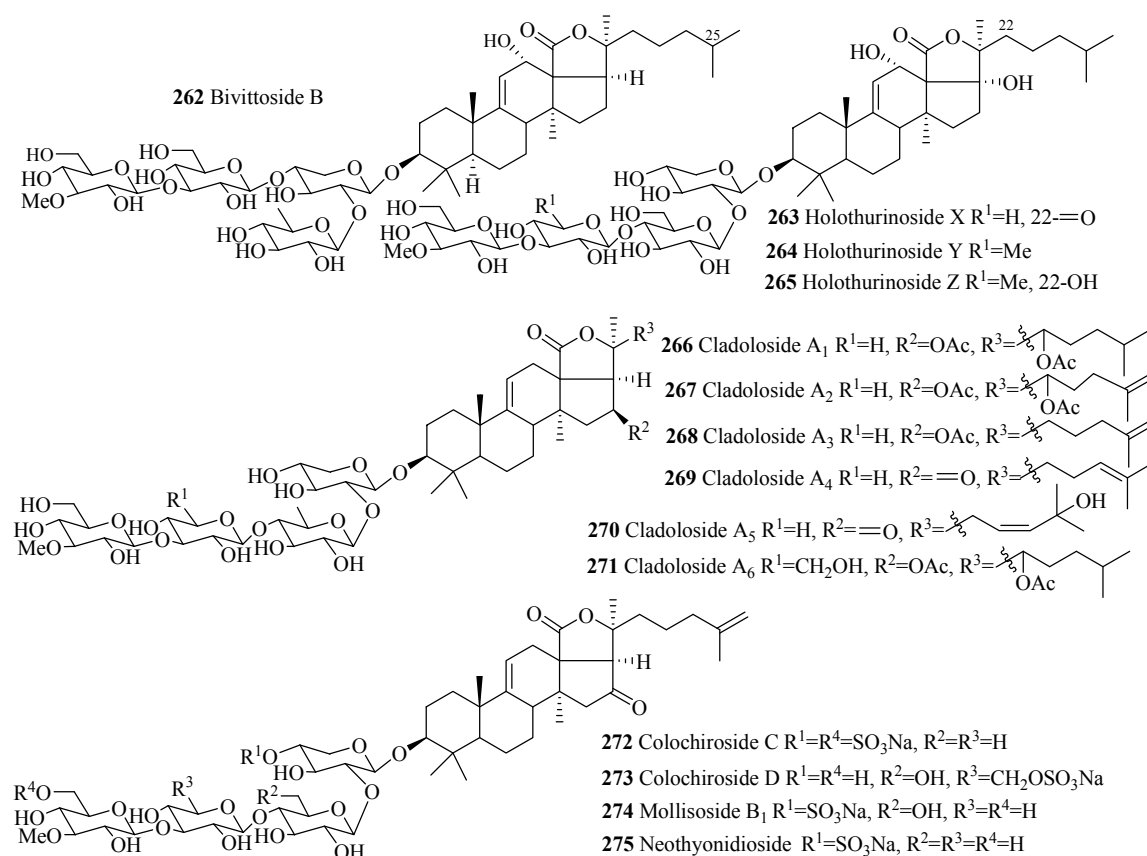


Figure 11. Chemical structures of holostane glycosides with 3 β -hydroxyholost-9(11)-ene and four sugar units.

Holostane Glycosides with 3 β -Hydroxyholost-9(11)-ene Skeleton and 1–3 Sugar Units

Only one type of carbohydrate chain, D-xylose-D-quinovose, is found in all glycosides in this group having two monosaccharide units (278–290), except 291 where carbohydrate chain is D-xylose-D-xylose (Figure 12 and Table 8); sulfate groups at C-4 of xylose units are also commonly found as well, except 285, 288 and 291. Hydroxy groups at either C-12 or C-17, or both positions, are observed in all the compounds in this category (Figure 12), except cercodemasaoides (276–279).

Table 8. Name and producing species of glycosides with 3 β -hydroxyholost-9(11)-ene and 1–3 sugar units.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|---------------------------------|------------------------------|-----------|---------------------------------|-------------------------|-----------|
| Cercodemasoide B (276) | <i>Cercodemas anceps</i> | [100] | Cercodemasoide C (277) | <i>C. anceps</i> | [100] |
| Cercodemasoide D (278) | <i>C. anceps</i> | [100] | Cercodemasoide E (279) | <i>C. anceps</i> | [100] |
| Holothurin B (280) | <i>Holothuria lessoni</i> | [119] | Holothurin B ₁ (281) | <i>H. lessoni</i> | [120] |
| Holothurin B ₂ (282) | <i>H. polii</i> | [121] | Holothurin B ₃ (283) | <i>H. polii</i> | [121] |
| Holothurin B ₄ (284) | <i>H. polii</i> | [121] | Holothurinoside D (285) | <i>H. forskalii</i> | [93] |
| Leucospilotaside A (286) | <i>H. leucospilota</i> | [122] | Leucospilotaside B (287) | <i>H. leucospilota</i> | [122] |
| Bivittoside A (288) | <i>Bohadschia bivittata</i> | [85] | Echinoside B (289) | <i>A. echinites</i> | [108] |
| 24-dehydroechinoside B (290) | <i>Actinopyga mauritiana</i> | [123] | Hillaside C (291) | <i>Holothuria hilla</i> | [124] |
| Hillaside B (292) | <i>H. hilla</i> | [81] | | | |

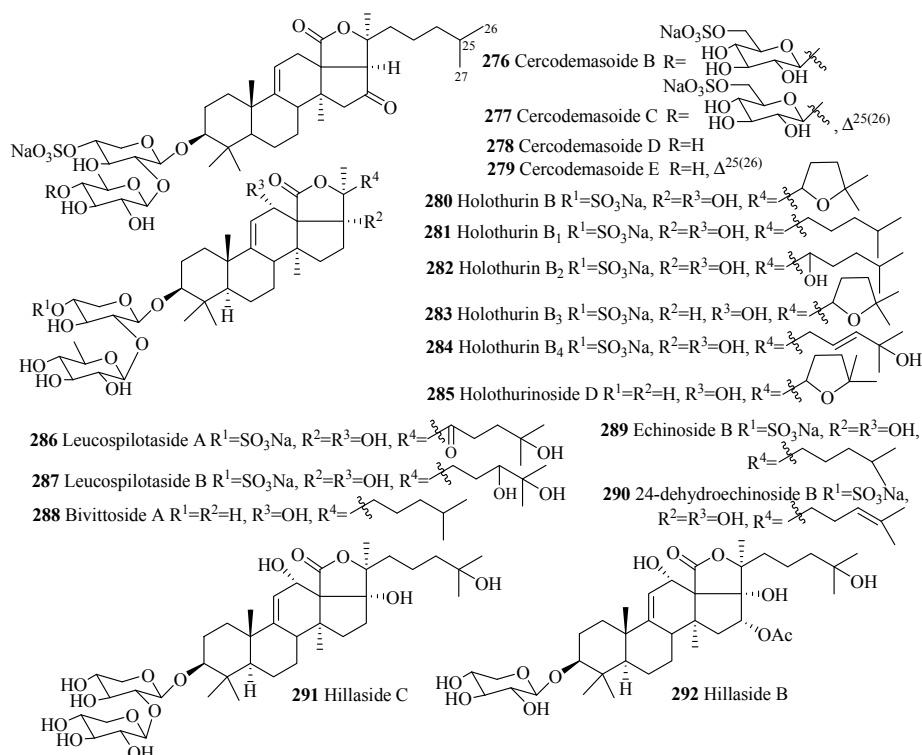


Figure 12. Chemical structure of holostane glycosides with 3β-hydroxyholost-9(11)-ene and 1–3 sugar units.

4.1.3. Holostane Glycosides with 3β-Hydroxyholost-8(9)-ene Skeleton

Only three glycosides belong to this group with carbohydrate chain consisting of 4–5 monosaccharide units (Table 9 and Figure 13). Among holostane sea cucumber glycosides, only one glycoside, synaptoside A₁ (293), contains keto group at C-7.

Table 9. Name and producing species of holostane glycosides with 3β-hydroxyholost-8(9)-ene skeleton.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|----------------------------------|-----------------------------|-----------|-----------------------|-----------------------------|-----------|
| Synaptoside A ₁ (293) | <i>Synapta maculata</i> | [41] | Variegatuside B (294) | <i>Stichopus variegates</i> | [73] |
| Variegatuside D (295) | <i>Stichopus variegates</i> | [21] | | | |

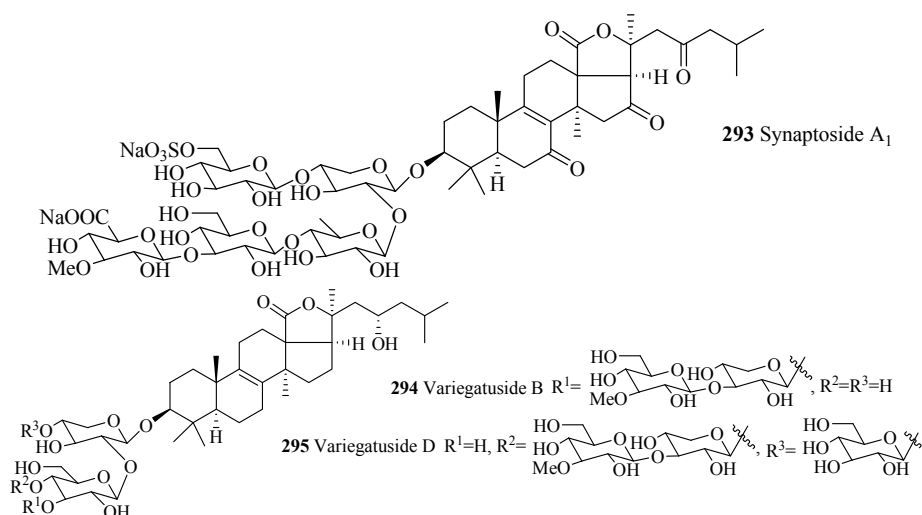


Figure 13. Chemical structures of holostane glycosides with 3β-hydroxyholost-8(9)-ene skeleton.

4.2. Nonholostane Glycosides

As mention earlier, like holostane glycosides, nonholostane glycosides do not have $\gamma(18,20)$ -lactone structural unit (Figures 14 and 15, Table 10). There are six different structural units (Figure 14) present in D- and E rings of aglycone in nonholostane glycosides. The aglycone side chain can be long or short, and may contain keto, methylene, hydroxy and acetoxy functional groups (Figure 15). Instead of $\gamma(18,20)$ -lactone, some glycosides in this group contain $\gamma(16,18)$ -lactone (296–300, 314, 322, 332–340 and 341). Cucumariosides A₈ (305) and A₉ (306) contain uncommon hydroxy group at C-18. Fallaxosides B₁ (322) and D₃ (327) are novel glycosides with unprecedented skeletons of aglycones. Psolusoside B (314) and Kuriloside C (316) have four members sugar architecture which are uncommon in both holostane and nonholostane glycosides. Another uncommon feature of this group of compounds is the presence of keto group at C-11 (323 and 325). Sulfate group is commonly found at C-4 of first xylose unit (Figure 15). Most of the nonholostane glycosides have branched five members carbohydrate chain (Figure 15).

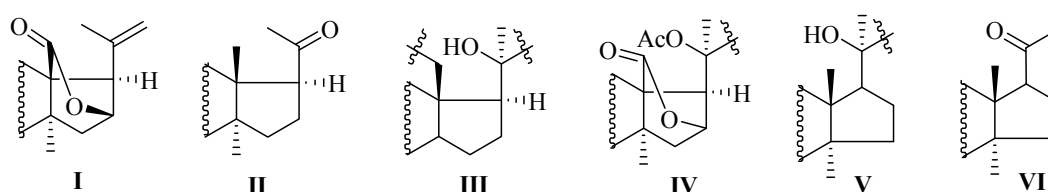


Figure 14. D- and E-ring structural architectures present in nonholotane glycosides.

Table 10. Name and producing species of nonholostane glycosides.

| Compound Name | Producing Species | Reference | Compound Name | Producing Species | Reference |
|--------------------------------------|--------------------------|-----------|--------------------------------------|--------------------------|-----------|
| Cucumarioside G ₂ (296) | <i>E. fraudatrix</i> | [125] | Cucumarioside A ₁₀ (297) | <i>E. fraudatrix</i> | [67] |
| Calcigeroside B (298) | <i>P. calcigera</i> | [37] | Calcigeroside C ₁ (299) | <i>P. calcigera</i> | [37] |
| Cucumarioside H ₃ (300) | <i>E. fraudatrix</i> | [30] | Cucumarioside A ₃₋₂ (301) | <i>C. conicospermium</i> | [26] |
| Cucumarioside A ₃₋₃ (302) | <i>C. conicospermium</i> | [26] | Koreoside A (303) | <i>C. koraiensis</i> | [126] |
| Isokoreoside A (304) | <i>C. conicospermium</i> | [26] | Cucumarioside A ₈ (305) | <i>E. fraudatrix</i> | [67] |
| Cucumarioside A ₉ (306) | <i>E. fraudatrix</i> | [67] | Holotoxin F (307) | <i>A. japonicus</i> | [22] |
| Holotoxin G (308) | <i>A. japonicus</i> | [22] | Holotoxin H (309) | <i>S. japonicus</i> | [127] |
| Holotoxin I (310) | <i>S. japonicus</i> | [127] | Ds-penaustroside A (311) | <i>P. australis</i> | [99] |
| Ds-penaustroside B (312) | <i>P. australis</i> | [99] | Frondoside C (313) | <i>C. frondosa</i> | [128] |
| Psolusoside B (314) | <i>Psolus fabricii</i> | [129] | Kuriloside A (315) | <i>D. kurilensi</i> | [130] |
| Kuriloside C (316) | <i>D. kurilensi</i> | [130] | Frondoside A ₂₋₇ (317) | <i>C. frondosa</i> | [36] |
| Frondoside A ₂₋₈ (318) | <i>C. frondosa</i> | [36] | Frondoside A ₇₋₃ (319) | <i>C. frondosa</i> | [43] |
| Frondoside A ₇₋₄ (320) | <i>C. frondosa</i> | [43] | Isofrondoside C (321) | <i>C. frondosa</i> | [43] |
| Fallaxoside B ₁ (322) | <i>C. fallax</i> | [131] | Fallaxoside C ₁ (323) | <i>C. fallax</i> | [132] |
| Fallaxoside C ₂ (324) | <i>C. fallax</i> | [132] | Fallaxoside D ₁ (325) | <i>C. fallax</i> | [132] |
| Fallaxoside D ₂ (326) | <i>C. fallax</i> | [132] | Fallaxoside D ₃ (327) | <i>C. fallax</i> | [131] |
| Fallaxoside D ₄ (328) | <i>C. fallax</i> | [133] | Fallaxoside D ₅ (329) | <i>C. fallax</i> | [133] |
| Fallaxoside D ₆ (330) | <i>C. fallax</i> | [133] | Fallaxoside D ₇ (331) | <i>C. fallax</i> | [133] |
| Magnumoside A ₁ (332) | <i>Massinium magnum</i> | [134] | Magnumoside A ₂ (333) | <i>M. magnum</i> | [134] |
| Magnumoside A ₃ (334) | <i>M. magnum</i> | [134] | Magnumoside A ₄ (335) | <i>M. magnum</i> | [134] |
| Magnumoside B ₁ (336) | <i>M. magnum</i> | [134] | Magnumoside B ₂ (337) | <i>M. magnum</i> | [134] |
| Magnumoside C ₁ (338) | <i>M. magnum</i> | [134] | Magnumoside C ₂ (339) | <i>M. magnum</i> | [134] |
| Magnumoside C ₄ (340) | <i>M. magnum</i> | [134] | Colochiroside E (341) | <i>C. robustus</i> | [135] |

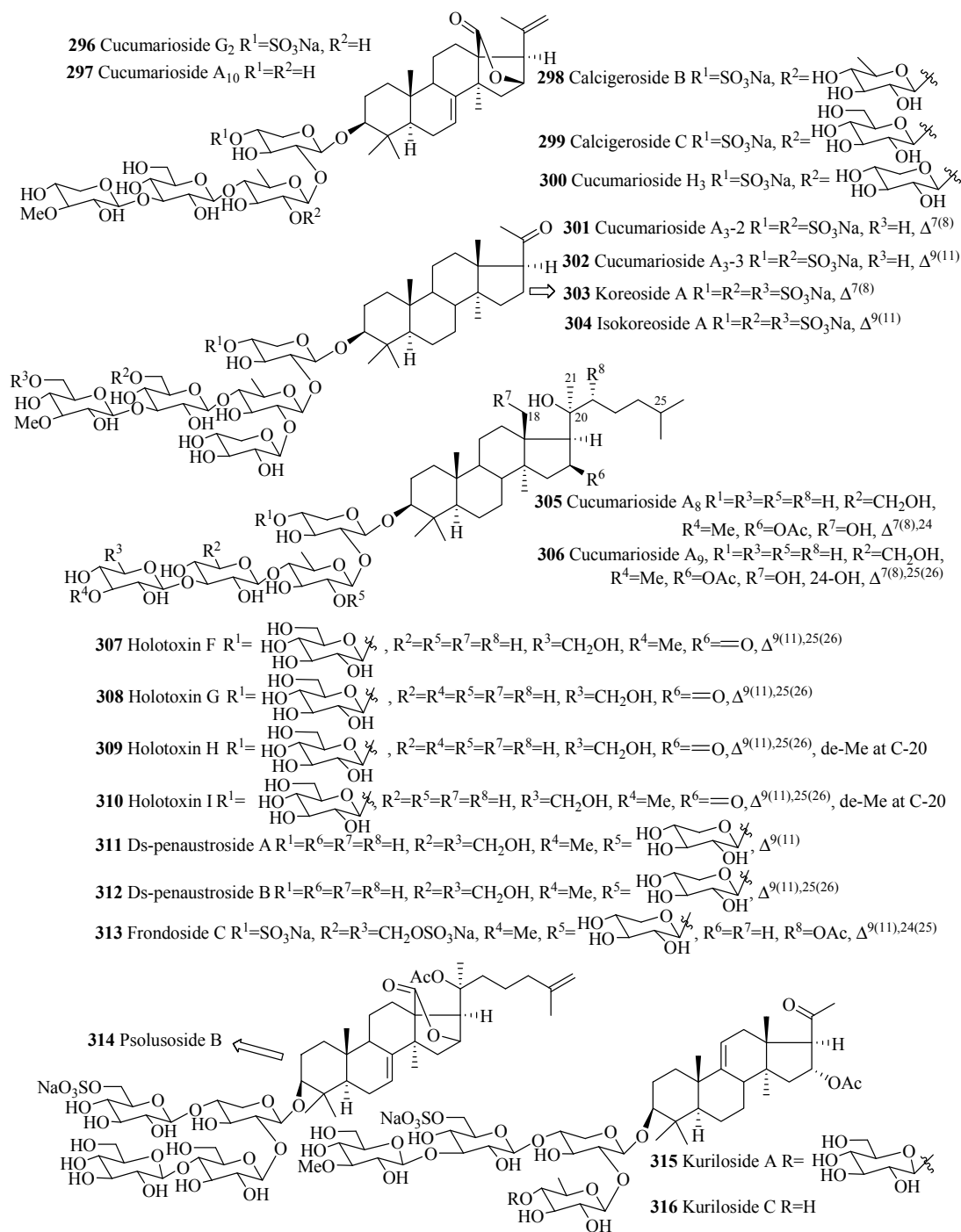


Figure 15. Cont.

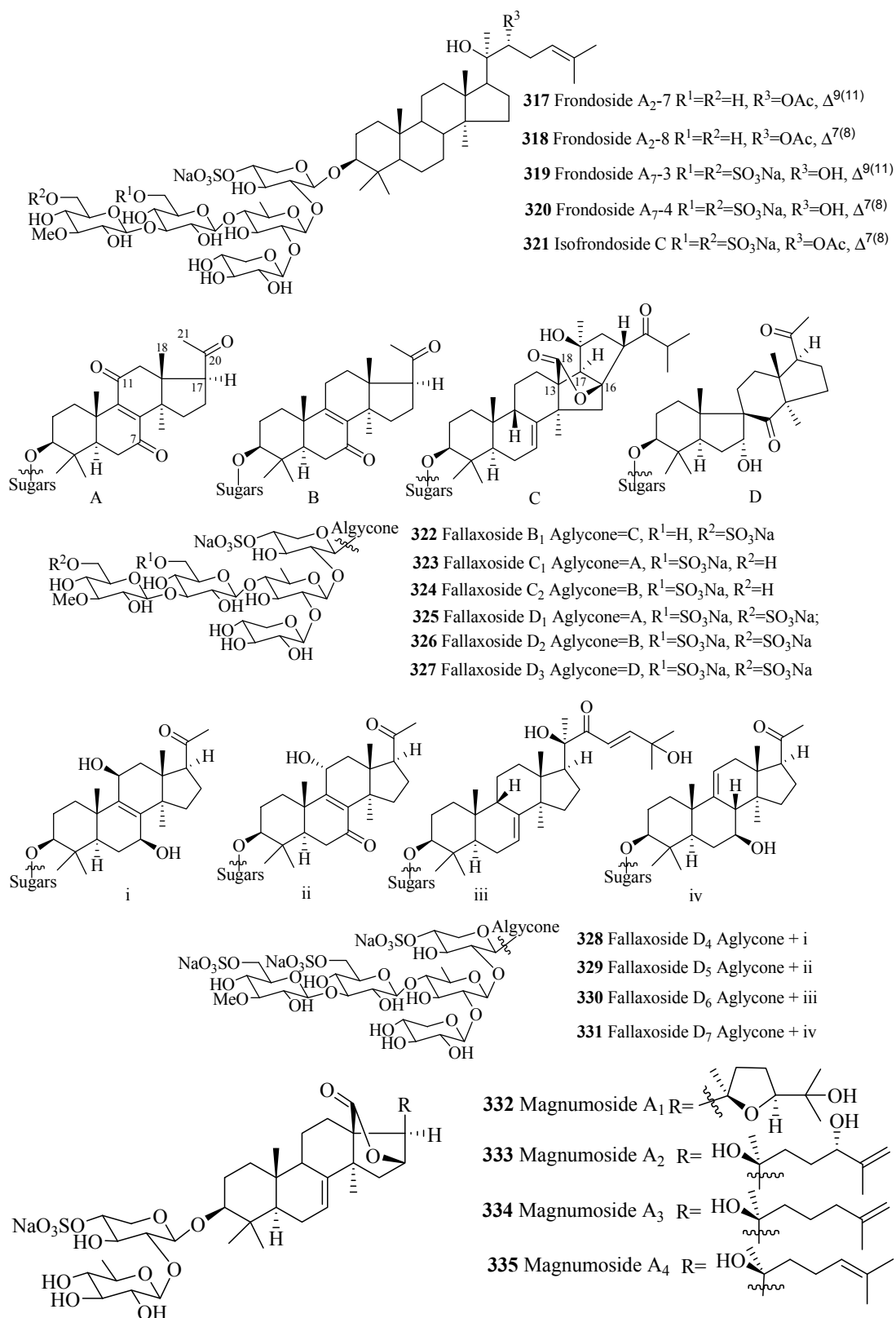


Figure 15. Cont.

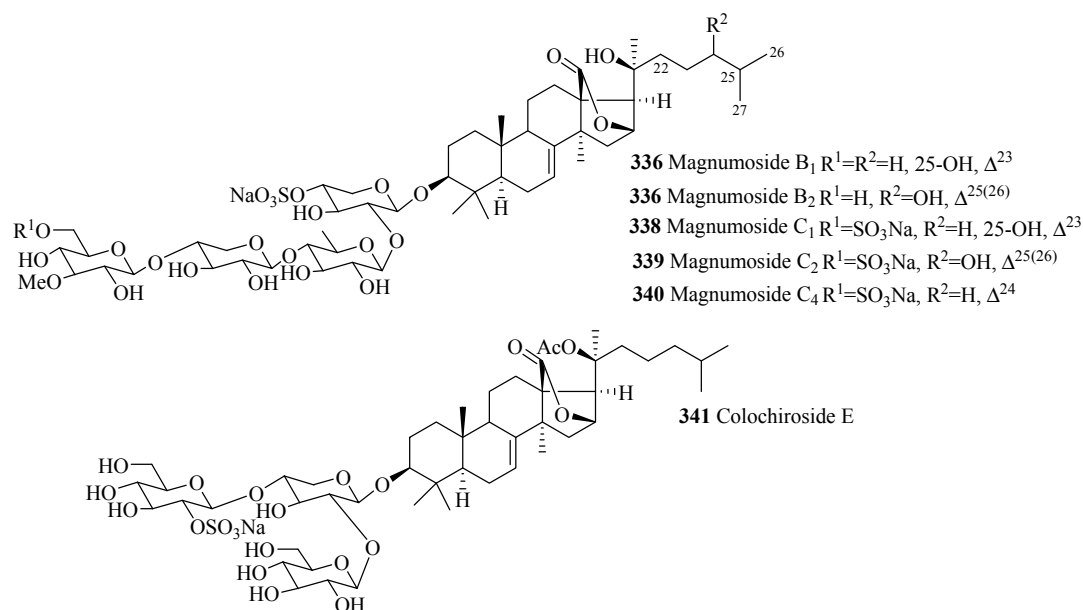


Figure 15. Chemical structures of nonholostane glycosides.

5. The Important Biological Properties of Sea Cucumber Glycosides

Triterpene glycosides are the prime bioactive metabolites of sea cucumbers, and are commonly known as toxins of sea cucumbers to eukaryotic cells. These glycosides showed a wide range of biological activities including cytotoxic, antifungal, antiviral, hemolytic, antiprotozoal and immunomodulatory activities. Sea cucumbers produce some major glycosides in sufficient amount to carry out a wide range of biological activity tests [37,94]. Besides major glycosides, they also produce minor glycosides insufficient to test a range of biological activities [66,67]. The point to be noted here is that sea cucumber glycosides are able to exhibit biological activities in both in vitro and in vivo models [5]. The remarkable biological properties showed by some triterpene glycosides are summarized in Table 11. Triterpene glycosides do not exhibit antibacterial activity, indicating that these glycosides are probably produced by sea cucumbers for defence against eukaryotic predators.

Table 11. Remarkable biological activities exhibited by some sea cucumber glycosides.

| Compound | Activity | Against/For | Activity Result | Reference |
|--------------------------------------|------------------|---------------------------------|---|-----------|
| Hillaside C (285) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.15–3.20 µg/mL | [124] |
| Hemoiedemside A (251) | Antifungal | <i>C. cucumerinum</i> | 20 µg/disc: 23 mm zone | [113] |
| Fuscocineroside C (237) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.88 and 0.58 µg/mL | [106] |
| Intercedenside A (66) | Cytotoxic | Human tumor cell lines | ED ₅₀ : 0.96–4.0 µg/mL | [49] |
| Intercedenside B (67) | Cytotoxic | Human tumor cell lines | ED ₅₀ : 0.61–2.0 µg/mL | [49] |
| Intercedenside C (68) | Cytotoxic | Human tumor cell lines | ED ₅₀ : 0.96–4.0 µg/mL | [49] |
| Holothurinoside A (195) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.33–0.71 µg/mL | [93] |
| Holothurinoside C (229) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.16–0.93 µg/mL | [93] |
| Liouvilloside A (53) | Virucidal | Herpes simplex virus | <10 µg/mL | [44] |
| Leucospilotaside B (281) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.44–2.62 µg/mL | [122] |
| Arguside B (164) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.38–2.60 µg/mL | [87] |
| Arguside C (165) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.38–2.60 µg/mL | [87] |
| Philinopside A (78) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 1.70–3.50 µg/mL | [52] |
| Philinopside B (79) | Cytotoxic | Human tumor cell lines | IC ₅₀ : 0.75–3.0 µg/mL | [53] |
| Cucumarioside A ₂ -2 (18) | Hemolytic | Erythrocyte of mouse | ED ₅₀ : 0.87 at 10 ⁻⁶ M | [136] |
| Holothurin B (274) | Antifungal | <i>T. mentagrophytes</i> | MIC-1.5 µg/mL | [137] |
| Holothurin A ₃ (227) | Cytotoxic | Human tumor cell lines | IC ₅₀ = 0.32–0.87 µg/mL | [103] |
| Holothurin A ₄ (228) | Cytotoxic | Human tumor cell lines | IC ₅₀ = 0.57–1.12 µg/mL | [103] |
| Scabraside A (230) | Antifungal | Eight pathogenic fungal strains | MIC ₈₀ : 2–8 µg/mL | [138] |
| Echinopside A (238) | Antifungal | Eight pathogenic fungal strains | MIC ₈₀ : 1–8 µg/mL | [108] |
| Cucumarioside A ₂ -2 (18) | immunomodulatory | Increased lysosomal activity | 0.2–20 ng/mouse | [139] |
| Fronoside A (37) | immunomodulatory | Enhanced phagocytosis | 0.001 µg/mL | [140] |
| Philinopside E (80) | Cytotoxicity | Ten tumor cell lines | ED ₅₀ : 0.75–3.50 µg/mL | [54] |
| Holotoxin A ₁ (152) | Antifungal | Five pathogenic fungi | MIC: 0.5–1.0 µg/mL | [22] |
| Cucumarioside A ₁ (106) | Hemolytic | Mouse erythrocytes | MEC ₁₀₀ : 0.7 ± 0.1 µg/mL | [66] |

6. Mechanisms of Action

Natural products derived from marine organisms have incredible structural and functional diversity. The mechanism by which triterpene glycosides exhibit anticancer activity primarily involve induction of tumor cell apoptosis through the activation of intracellular caspase cell death pathways, arrest of the cell cycle at S or G₂/M phases and increase of the sub-G₀/G₁ cell population; regulation of nuclear factor NF- κ B expression; reduction in cancer cell adhesion; suppression of cell migration and tube formation; suppression of angiogenesis; inhibition of cell proliferation, colony formation, and tumor invasion [141]. However, the detailed mechanism(s) of the anticancer activities of these glycosides remains largely unclear.

Marked membranolytic effects such as increased membrane permeability, loss of barrier function, and the rupture of cell membrane are considered the basic mechanisms underlying a variety of biological activities exerted by triterpene glycosides of sea cucumbers. The glycosides form complex with $\Delta^{5(6)}$ -sterols of cellular membrane especially cholesterol. This interaction induces significant changes in the physicochemical properties of cell membranes, such as variations in their stability, microviscosity, and permeability. Saponins form complexes with membrane sterols, leading to cell disruption by the formation of pores. Due to this irreversible interaction, the selective permeability of cell membranes is impaired and cell compounds are transferred into the extracellular matrix, ultimately resulting in cell death [142,143].

7. Structure–Activity Relationships (SARs)

Both glycone and aglycone parts are important for biological activities of sea cucumber glycosides. The structure–activity relationships among sea cucumber glycosides are presumably more complicated. The most important structural characteristics of glycosides that probably contribute in biological activities are mentioned below.

The cytotoxicity not only depends on the chemical structures of the glycosides but also cell types [144]. The presence of 12 α -hydroxy and 9(11)-ene structural units in holostane aglycone play key role in cytotoxicity [144]. Number of monosaccharide units in sugar chains and the substitution in side chain of aglycone could affect cytotoxicity. The presence of hydroxy groups in the side chains of glycosides significantly reduces cytotoxicity of the glycosides with increasing distance of hydroxy group from the 18(20)-lactone [30,31]. Linear tetraoside unit plays important role in different biological activities of sea cucumber glycosides [144]. Hexaoside chain containing glycosides show stronger cytotoxic activity than pentaoside chain containing glycosides. Glycosides with hexaosides residue with xylose or quinovose in the fifth position are the most active cytotoxins [144]. Different activities test result indicates that the number of sulfate groups and their position in the carbohydrate chains affect cytotoxicity [144]. It has been shown that the sulfate group attached to C-6 of terminal 3-O-methylglucose unit greatly decrease and attached to C-6 of glucose (the third monosaccharide unit) generally increase membranotropic activity [145].

8. Conclusions

Sea cucumbers (or holothurians), a class of marine invertebrates, are used as human food and traditional medicine, especially in some parts of Asia. The majority of the sea cucumbers synthesize glycosides with a polycyclic aglycone that contain either 7(8)- or 9(11)-double bond with up to six monosaccharide residues containing carbohydrate chain. A few of them are known to synthesize aglycone with 8(9)-ene. Sea cucumber glycosides are cytotoxic to eukaryotes; probably produce for escaping from predation by marine eukaryotic organisms. These cucumber metabolites have shown profound cytotoxic and hemolytic activities against eukaryotic organisms but not prokaryotic organisms. Due to significant cytotoxic and antifungal activities, extensive differential SAR studies of these glycosides can be helpful to develop new drugs and agrochemicals.

Acknowledgments: We are also thankful to the World Bank for partial funding of this work through a subproject of Higher Education Quality Enhancement Project (HEQEP), Supplementary Complete Proposal #2071. This research was also supported in part by the Ministry of Oceans and Fisheries (Grant PM60300), Korea. Sincere thanks are due to Prodip Kumar Roy of OIST, Okinawa, Japan for help in literature collection.

Conflicts of Interest: The authors declare no conflict of interest.

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