REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Genus *Holothuria* an imminent source of diverse chemical entities: A review

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Abstract

Nature is a valuable source for many medicines in use. About 30 per cent of the world's drugs are either natural products or their biologically active derivatives. Natural products display a wide range of chemical structures that even are unapproachable by highly formulated synthetic principles. Compared to the terrestrial, marine organisms have provided the widest diversity; thirty-four of the thirty-six phyla of life exist. One of the most important diverse families of sea cucumbers is the Holothuriidae family, which exist in oceans and shallow waters as well. This family comprises five genera. Among them, genus *Holothuria* which is the most predominant one and represented in Egypt by eight species. Phytochemical investigation of sea cucumbers belonging to genus *Holothuria* has led to the isolation and identification of numerous chemical compounds of different classes. The current review demonstrated that genus *Holothuria* is a rich source of cerebrosides, saponins, fatty acids, amino acids and phenolics.

Keywords: *Holothuria***,** *Sea cucumber***,** *Secondary metabolites*

1.Introduction:

Nature is a major source for many medicines in use. About 30 per cent of the world's drugs are either natural products or their biologically active derivatives. Natural products display a wide range of chemical structures that even are unapproachable by highly formulated synthetic principles. In addition, phytochemicals have introduced novel therapeutic approaches which helped to make new biochemical approaches **(Grabley and Sattler, 2003)**. Compared to the terrestrial ecosystems, marine organisms have provided the widest diversity; thirty-four of the thirty-six phyla of life exist. About 70 per cent of the surface of our planet is occupied by oceans that provide invertebrates with a diverse living climate **(Lalli and Parsons, 1993).** This incredible biodiversity has provided an amazing chemical library for marine natural products with a wide range of bioactivities (**Haefner *et al.*, 2003**). Holothuroidea class (sea cucumber) includes nearly 1,400 species of six orders worldwide (Apodida, Aspidochirotida, Elasipodida, Molpadiida, Dendrochirotida, and

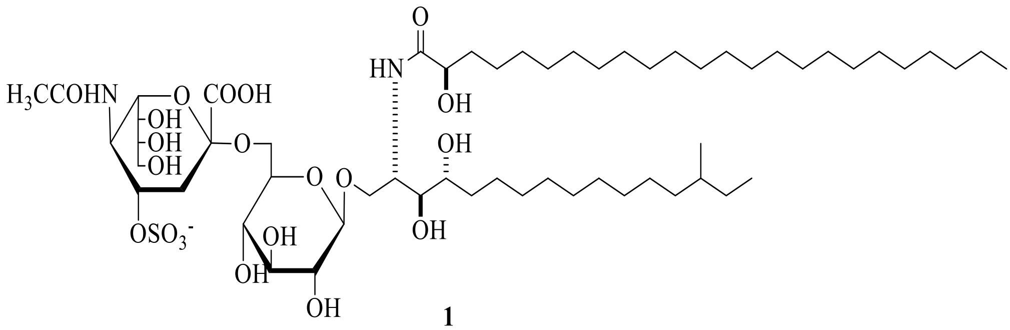
Dactylochirotida) and 25 families (**Mohammed *et al*., 2016**). Sea cucumbers are present in all oceans worldwide; they exist on the ocean floor or near it, and are frequently hidden beneath it. Additionally, they are found in shallow waters as well. Oriental people, mainly the Japanese and Chinese, use sea cucumbers as a source of medicine and food, resulting in large-scale annual harvesting of sea cucumbers, which contributed to the extinction of many species **(Ceesay *et al*., 2012).** One of the most important diverse families of sea cucumbers is the Holothuriidae family. This taxon comprises five genera **(Honey-Escandón *et al*., 2015)**. Among them, genus *Holothuria* which is the most predominant one according to the database in World Register of Marine Species **(http://www.marinespecies.org/)** and it is represented in Egypt by eight species **(Ahmed *et al*., 2016)**. Phytochemical investigation of *Holothuria* sea cucumbers has led to the isolation and identification of numerous bioactive phytoconstituents of diverse chemical classes (**Bordbar *et al*., 2011**). Based on the aforementioned reports, the aim of this review is to provide a comprehensive update on the chemistry of sea cucumbers belonging to genus *Holothuria.*

2. Chemical constituents reported from some species of genus *Holothuria*:

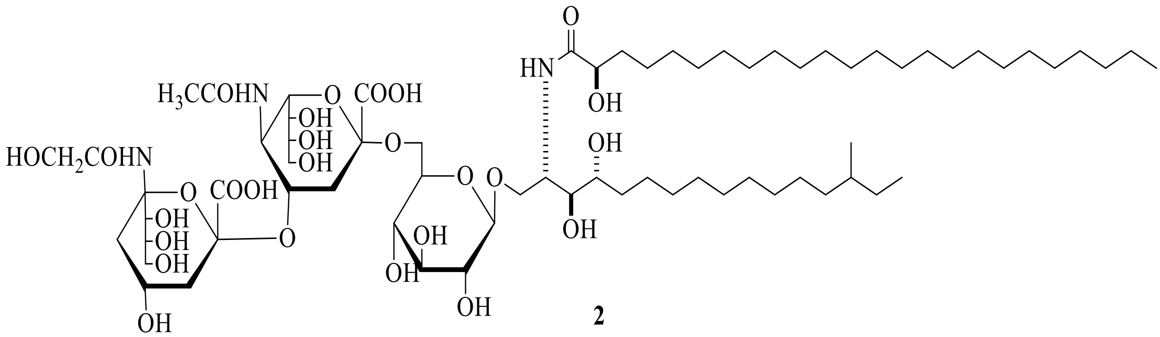
2.1: Cerebrosides: Numerous cerebrosides have been isolated in genus *Holothuria* (Table 1)

Table 1: Cerebrosides reported in genus *Holothuria*.

Compound No	Species	Compound Name	Reference
1	*H. pervicax*	HPG-8	**(Yamada *et al*., 1998)**.
2	*H. pervicax*	HPG-3	**(Yamada *et al*., 1998).**
3	*H. pervicax*	HPG-1	**(Yamada *et al*., 1998).**
4	*H. pervicax*	HPG-7	**(Yamada *et al*., 2000)**
5	*H. pervicax*	HPC-1	**(Yamada *et al*., 2002)**
6	*H. pervicax*	HPC-2	**(Yamada *et al*., 2002)**
7	*H. pervicax*	HPC-3-A and HPC-3-B	**(Yamada *et al*., 2002)**
8	*H. pervicax*	HPC-3-C - HPC-3-J	**(Yamada *et al*., 2002)**
9	*H. Leucospilota*	HLG-1	**(Yamada *et al*., 2001)**
10	*H. Leucospilota*	HLG-2	**(Yamada *et al*., 2001)**
11	*H. Leucospilota*	HLG-3	**(Yamada *et al*., 2001)**
12	*H. Leucospilota*	HLC-2-A	**(Yamada *et al*., 2005)**
13	*H. coronopertusa*	Compound-1-a, Compound-1-b, Compound-2-a, Compound-2-b, Compound-2-c, Compound-3-a, Compound-3-b, Compound-3-c, Compound-3-d, Compound-4-a, Compound-4-b, Compound-4-c, Compound-5-a, Compound-5-b, Compound-5-c, Compound-6-a, Compound-6-b and Compound-6-c	**(Hue *et al*., 2001)**



1



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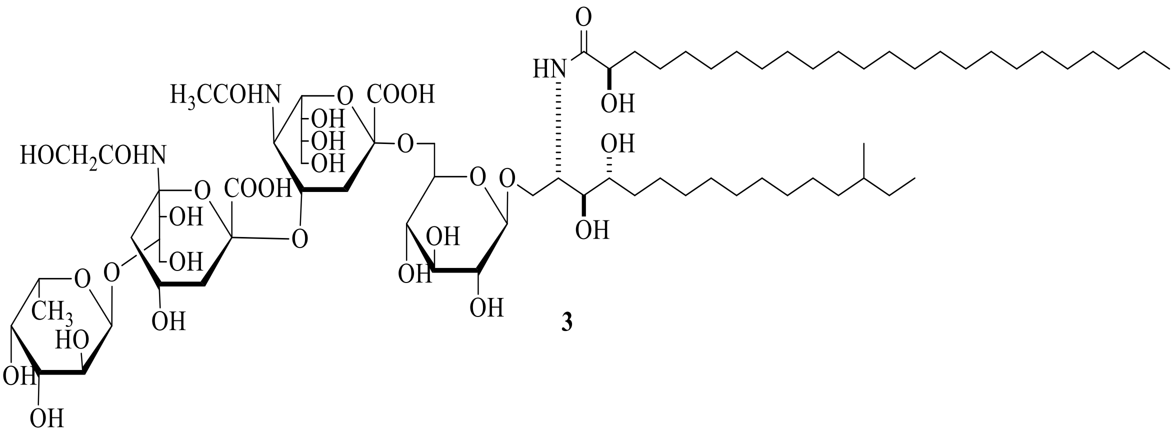

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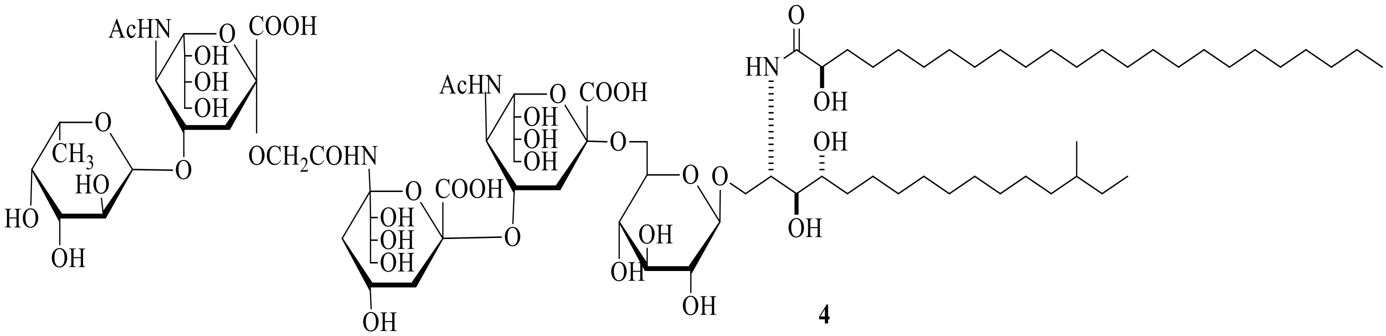
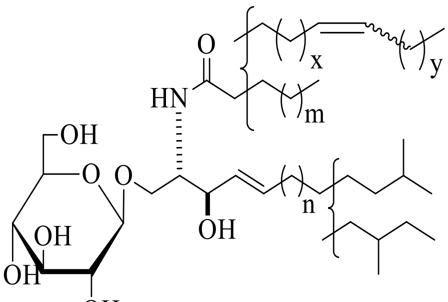


4

Figure 1: chemical structures of compounds 1-4

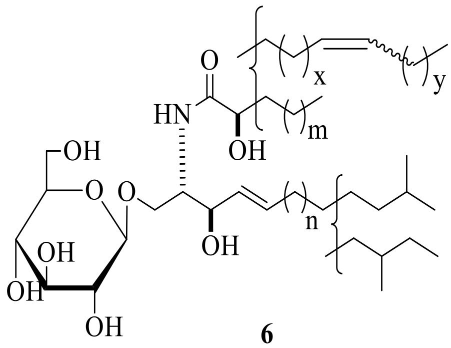


5

x + y = 18

m = 14, 18, 19

n = 6, 7, 8

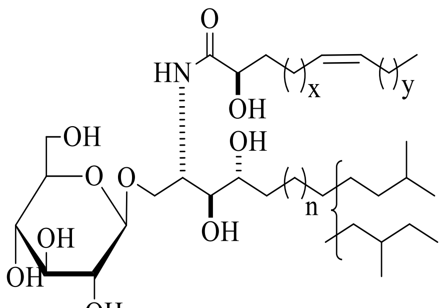


6

x + y = 18

m = 18, 19, 20

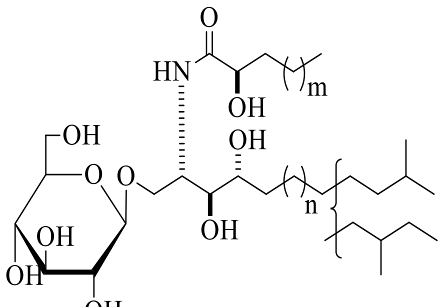
n = 6, 7, 8



7

HPC-3-A : x = 10, y = 7, n = 6

HPC-3-B : x = 11, y = 7, n = 6



8

HPC-3-C : m = 18, n = 6

HPC-3-D : m = 18, n = 7

HPC-3-E : m = 19, n = 6

HPC-3-F : m = 18, n = 8

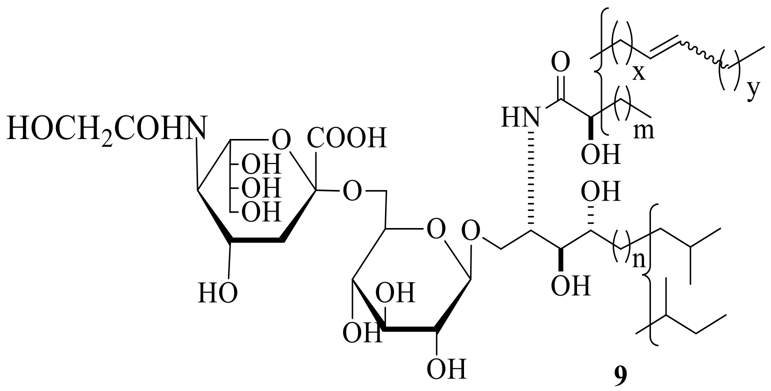
HPC-3-G : m = 19, n = 7

HPC-3-H : m = 20, n = 6

HPC-3-I : m = 19, n = 8

HPC-3-J : m = 20, n = 7

Figure 2: chemical structures of compounds 5-8.



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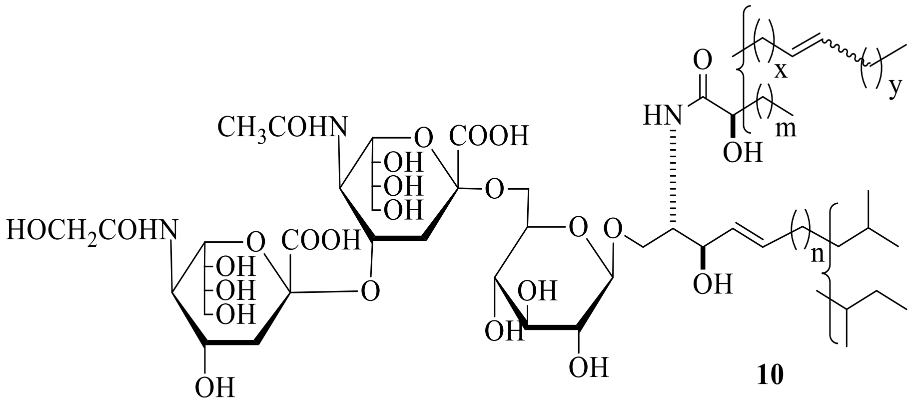

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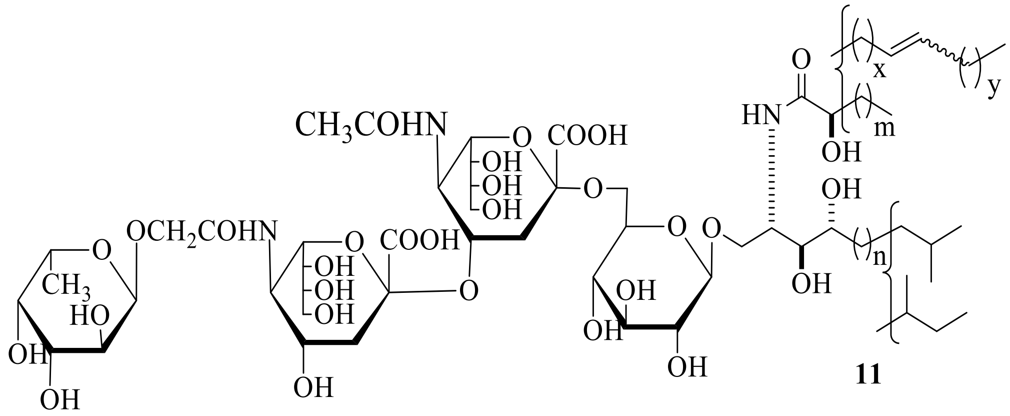
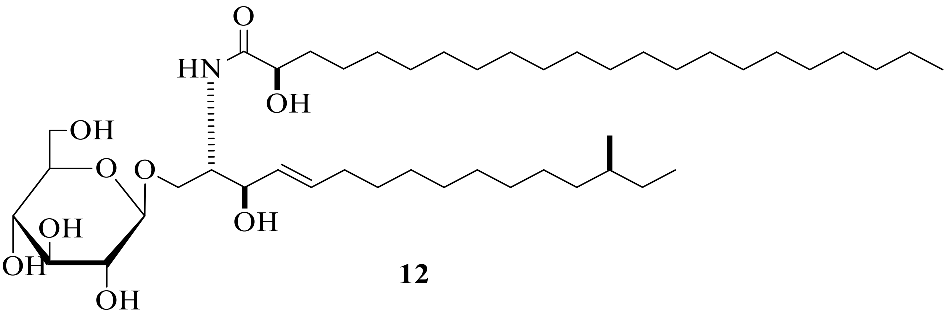
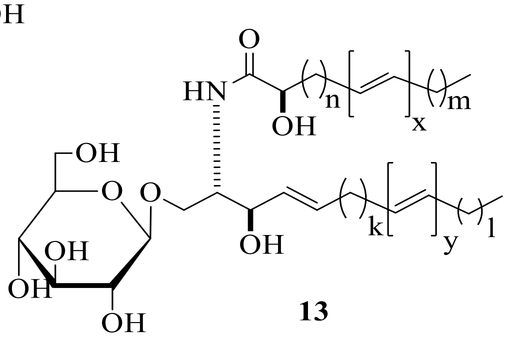


11

Figure 3: chemical structures of compounds 9-11.



12



13

Compound-1-a : n = 19, x = 0, m = 0, k = 11, y = 0, l = 0

Compound-1-b : n = 20, x = 0, m = 0, k = 10, y = 0, l = 0

Compound-2-a : n = 19, x = 0, m = 0, k = 12, y = 0, l = 0

Compound-2-b : n = 20, x = 0, m = 0, k = 11, y = 0, l = 0

Compound-2-c : n = 21, x = 0, m = 0, k = 10, y = 0, l = 0

Compound-3-a : n = 19, x = 0, m = 0, k = - , y = 1, l = -

Compound-3-b : n = -, x = 1, m = -, k = 12, y = 0, l = 0

Compound-3-c : n = 20, x = 0, m = 0, k = -, y = 1, l = -

Compound-3-d : n = 12, x = 1, m = 7, k = 11, y = 0, l = 0

Compound-4-a : n = 19, x = 0, m = 0, k = 13, y = 0, l = 0

Compound-4-b : n = 20, x = 0, m = 0, k = 12, y = 0, l = 0

Compound-4-c : n = 21, x = 0, m = 0, k = 11, y = 0, l = 0

Compound-5-a : n = -, x = 1, m = -, k = 13, y = 0, l = 0

Compound-5-b : n = 12, x = 1, m = 7, k = 12, y = 0, l = 0

Compound-5-c : n = -, x = 1, m = -, k = 11, y = 0, l = 0

Compound-6-a : n = 20, x = 0, m = 0, k = 13, y = 0, l = 0

Compound-6-b : n = 21, x = 0, m = 0, k = 12, y = 0, l = 0

Compound-6-c : n = 22, x = 0, m = 0, k = 11, y = 0, l = 0

Figure 4: chemical structures of compounds 12 and 13.

2.2: Saponins:

- Sea cucumber triterpene glycosides are categorized into two groups according to the existence or absence of γ (18-20) lactone in the glycoside aglycone portion based on their chemical structure. Triterpene glycosides containing 3β-hydroxy-5α-lanostano-γ (18, 20)-lactone are holostane type whereas non holostane type does not contain γ (18-20) lactone. Glycosides of the holostane type often vary in their aglycone chemical structure so that they can be further subdivided into three classes:

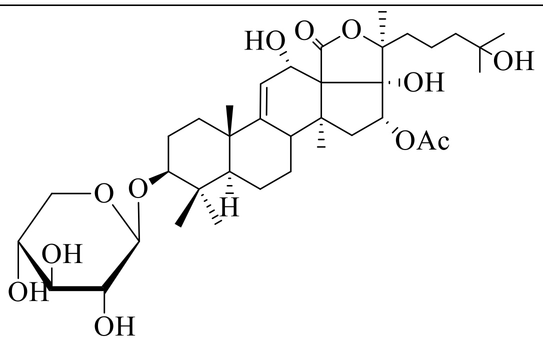
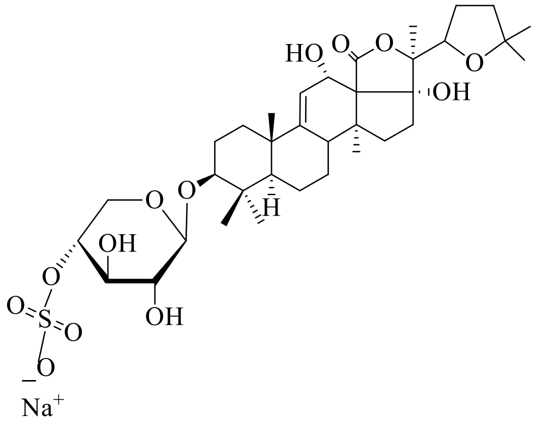
- Holostane glycosides contain 3β-hydroxyholost-9(11)-ene. See Tables (2,3,4,5 and 6)
- Holostane glycosides contain 3β-hydroxyholost-8(9)-ene.
- Holostane glycosides contain 3β-hydroxyholost-7(8)-ene.

Each of these three groups can also be further divided into additional groups or categories based on the number of sugar units in the holostane glycoside glycone structure **(Mondol *et al*., 2017).**

2.2.1- Holostane glycosides contain 3β-hydroxyholost-9(11)-ene:

2.2.1.1- Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 1-3 sugar units oligosaccharide chain:

Table 2: Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 1-3 sugar units oligosaccharide chain reported in genus *Holothuria*:

Species	Compound Name	Compound Structure	Reference
H. hilla	Hillaside B		**(Wu *et al*., 2007)**
H. leucospilota	Leucospilotaside C		**(Han *et al*., 2008)**.

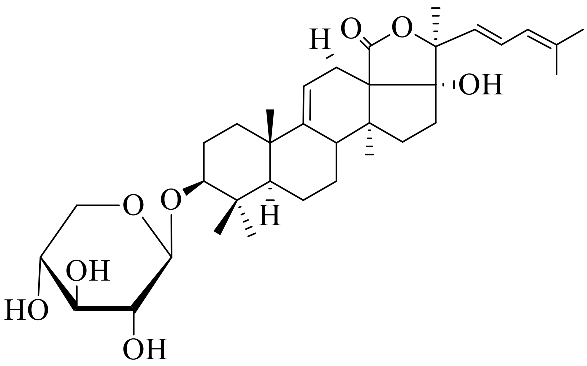
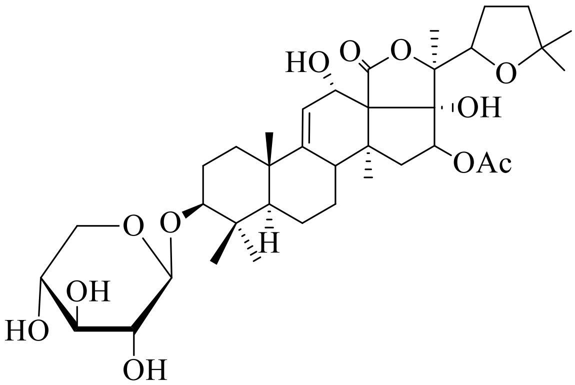
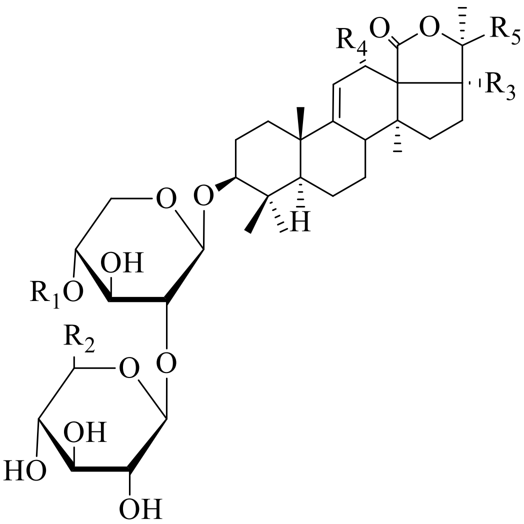
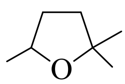
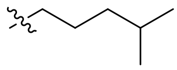
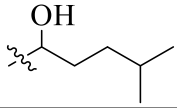
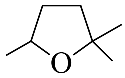
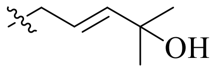
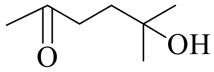
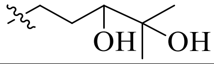
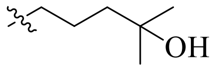
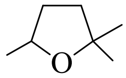
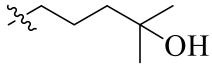
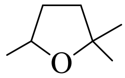
H. nobilis	Nobiliside A		**(Wu *et al.*, 2006a)**
H. nobilis	Nobiliside C		**(Wu *et al.*, 2006a)**

Table 3: Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 1-3 sugar units oligosaccharide chain reported in geuns *Holothuria*:



Species	**Compound Name**	**R^1**	**R^2**	**R^3**	**R^4**	**R^5**	**Reference**
H. lubrica, H.arenicola, H. pervicax, H. nobilis, H. hilla, H. gracilis, H. difficilis, H. coluber H. pulla. H. cubana,	Holothurin B	SO_3Na	CH_3	OH	OH		**(Yasumoto *et al.*, 1967), (Elyakov *et al.*, 1973), (Elyakov *et al.*, 1975), (Kitagawa *et al.*, 1979),**

H.grisea, H. surinamensis *H.mexicana, H.atra* *H.leucospilota, H.polii,* *H.axiloga, H.edulis,* *H.tubulosa, H. scabra* and *H. fuscocinerea*							**(Kobayashi *et al.*,1991),** **(Silchenko *et al.*, 2005),** **(Zhang *et al.*, 2006)** **(Dang *et al.*, 2007)**
H. leucospilota , H. atra	Holothurin B_1	SO_3Na	CH_3	OH	OH		**(Kitagawa *et al*., 1978)** **(Kobayashi *et al.*, 1991)**
H. polii	Holothurin B_2	SO_3Na	CH_3	OH	OH		**(Silchenko *et al.*, 2005)**
H. polii	Holothurin B_3	SO_3Na	CH_3	H	OH		**(Silchenko *et al.*, 2005)**
H. polii	Holothurin B_4	SO_3Na	CH_3	OH	OH		**(Silchenko *et al.*, 2005)**
H. leucospilota	leucospilotaside A	SO_3Na	CH_3	OH	OH		**(Hua *et al.*, 2009)**
H. leucospilota	leucospilotaside B	SO_3Na	CH_3	OH	OH		**(Hua *et al.*, 2009)**
H. leucospilota	leucospilotaside D	SO_3Na	CH_3	OH	OH		**(Honey-Escandón *et al.*, 2015)**
H. forskali	Holothurinoside D	H	CH_3	H	OH		**(Rodriguez *et al.*, 1991)**
H. hilla	Hillaside C	H	H	OH	OH		**(Wu et al., 2006b).**
H. nobilis	Nobiliside B	SO_3Na	CH_2OH	OH	H		**(Wu *et al.*, 2006a)**

2.2.1.2 Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 4 sugar units oligosaccharide chain

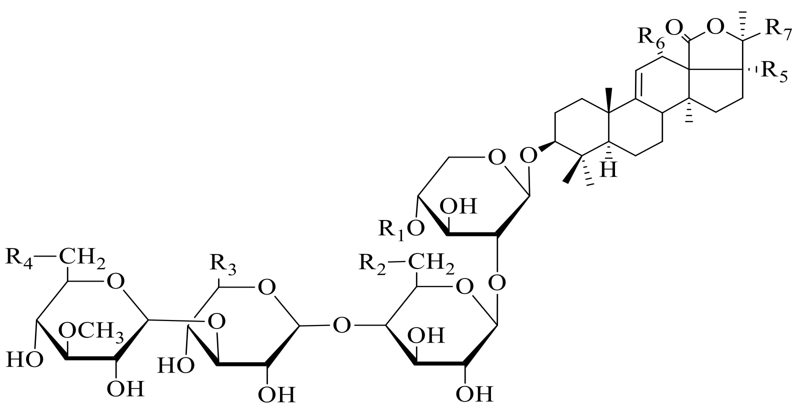
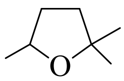
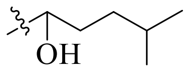
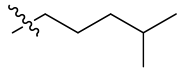
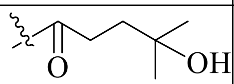
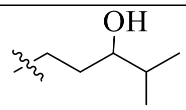
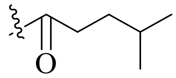
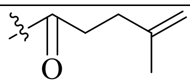
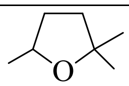
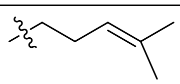
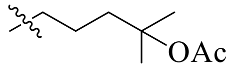
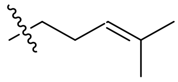
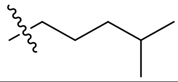
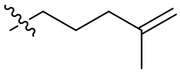
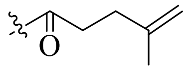
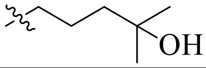
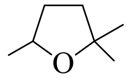
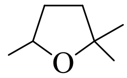
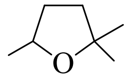
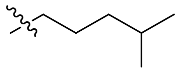
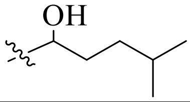
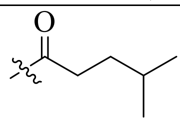


Table 4: Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 4 sugar units oligosaccharide chain reported in genus *Holothuria*:

Species	Compound Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Reference
H. lubrica H.arenicola, *H. pervicax, H. nobilis,* *H. hilla, H. gracili,* *H.difficilis, H. coluber* *H. pulla. H. cubana,* *H.grisea, H. surinamensis* *H.mexicana H.leucospilota* *H.atra H.axiloga* *H.edulis H.polii* *H.tubulosa H.fuscocinerea* *H. scabra*	Holothurin A	SO_3Na	H	CH_2OH	OH	OH	OH		**(Yasumoto *et al.*, 1967)** **(Elyakov *et al.*, 1973)** **(Elyakov *et al.*, 1975)** **(Kitagawa *et al.*, 1979)** **(Kobayashi *et al.*,1991)** **(Silchenko *et al.*, 2005)** **(Zhang *et al.*, 2006)** **(Dang *et al.*, 2007)**
H. floridana H. grisea	Holothurin A_1	SO_3Na	H	CH_2OH	OH	OH	OH		**(Stonik, 1986)** **(Elyakov *et al.*, 1975)**
H. edulis, *H. mauritana* *H.atra H. axiloga*	Holothurin A_2	SO_3Na	H	CH_2OH	OH	OH	OH		**(Caulier *et al.*, 2011)**
H. scabra	Holothurin A_3	SO_3Na	H	CH_2OH	OH	OH	OH		**(Dang et al., 2007)**
H. scabra	Holothurin A_4	SO_3Na	H	CH_2OH	OH	OH	OH		**(Dang *et al.*, 2007)**
H. fuscocinerea	Fuscocineroside A	SO_3Na	H	CH_2OH	OH	H	OH		**(Zhang *et al.*, 2006)**
H. fuscocinerea	Fuscocineroside B	SO_3Na	H	CH_2OH	OH	H	OH		**(Zhang *et al.*, 2006)**
H. fuscocinerea *H. scabra*	Fuscocineroside C	SO_3Na	H	CH_2OH	OH	H	OH		**(Zhang *et al.*, 2006)** **(Han *et al.*, 2012).**
H. scabra	24-dehydroechinoside A	H	H	CH_2OH	OH	OH	OH		**(Han *et al.*, 2012).**

H. pervicax	Pervicosides A	SO_3Na	H	CH_2OH	OH	H	OH		**(Kitagawa *et al.*, 1989)**
H. pervicax	Pervicosides B	SO_3Na	H	CH_2OH	OH	H	OH		**(Kitagawa *et al.*, 1989)**
H. pervicax	Pervicosides C	SO_3Na	H	CH_2OH	OH	H	OH		**(Kitagawa *et al.*, 1989)**
H. scabra	Scabraside A	SO_3Na	H	CH_2OH	OH	OH	OH		**(Han *et al*, 2009).**
H. scabra	Scabraside B	SO_3Na	H	CH_2OH	OH	OH	OH		**(Han *et al*, 2009).**
H. scabra	Scabraside D	SO_3Na	H	CH_2OH	OH	OH	OH		**(Han *et al.*, 2012).**
H. forskali	Holothurinoside C	H	H	CH_2OH	OH	H	OH		**(Rodriguez *et al.*, 1991).**
H. lesson	Holothurinoside J1	H	OH	CH_2OH	OH	OH	OH		**(Bahrami *et al.*, 2014)**
H. forskali	Holothurinoside C1	H	OH	CH_2OH	OH	H	H		(**Honey-Escandón *et al.***, **2015**)
H. lesson	Holothurinoside Y	H	OH	CH_3	OH	OH	OH		**(Bahrami *et al.*, 2014)**
H. lesson	Holothurinoside Z	H	OH	CH_3	OH	OH	OH		**(Bahrami *et al.*, 2014)**
H. lesson	Holothurinoside X	H	OH	H	OH	OH	OH		**(Bahrami *et al.*, 2014)**

2.2.1.3 Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 5 sugar units oligosaccharide chain:

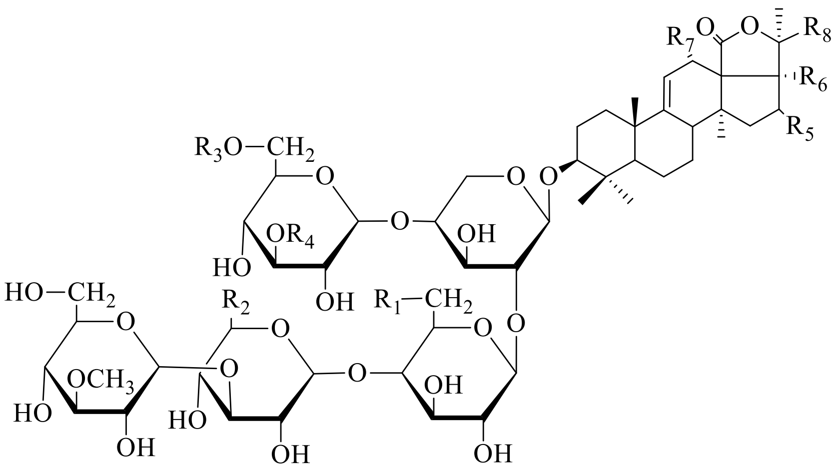
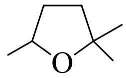
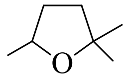
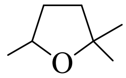
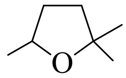
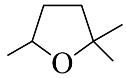
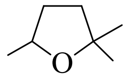
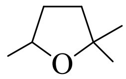
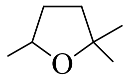
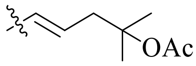
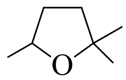
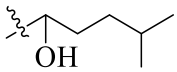
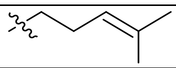
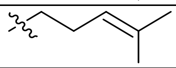
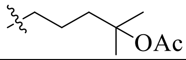


Table 5: Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 5 sugar units oligosaccharide chain reported in genus *Holothuria*:

Species	Compound Name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Reference
H forskalli	Holothurinoside A	H	CH_2OH	H	H	H	OH	OH		**(Rodriguez *et al.*, 1991)**
H. lesson *H. forskali*	Holothurinoside A_1	OH	CH_2OH	H	H	H	H	OH		(**Bahrami *et al.***, 2014) (**Rodriguez *et al.***, 1991)
H. lesson	Holothurinoside E	H	CH_2OH	H	H	H	H	OH		(**Bahrami *et al.***, 2014)
H. lesson	Holothurinoside E1	OH	CH_2OH	H	H	H	H	H		**(Bahrami *et al.*, 2014)**
H. lesson	Holothurinoside M	H	CH_2OH	H	CH_3	H	H	OH		**(Bahrami *et al.*, 2014)**
H. sanctori	Holothurinoside M_1	OH	CH_2OH	H	CH_3	H	H	H		**(Caulier *et al.*, 2016)**
H. forskali	Holothurinoside N (Holothurinoside L)	H	CH_2OH	H	CH_3	H	OH	OH		**(Honey-Escandón *et al.*, 2015)**
H. sanctori	Holothurinoside N_1	OH	CH_2OH	H	CH_3	H	H	OH		**(Caulier *et al.*, 2016)**
H. forskalli	Holothurinoside B	H	CH_2OH	H	H	H	OH	OH		**(Rodriguez *et al.*, 1991)**
H. grisea	17-dehydroxyholothurinoside A	H	CH_2OH	H	CH_3	H	H	OH		(**Sun *et al.***, **2008**).
H. grisea	Griseaside A	H	CH_2OH	H	H	H	H	OH		(**Sun *et al.***, **2008**).
H. axiloga	Impatienside B	H	CH_2OH	H	H	H	H	OH		**(Yuan *et al.*, 2009)**
H. axiloga	Arguside F	H	CH_2OH	H	H	OAc	H	OH		**(Yuan *et al.*, 2009)**
H. axiloga	Pervicoside D	H	CH_2OH	H	H	H	H	OH		**(Yuan *et al.*, 2009)**

2.2.1.3 Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 6 sugar units oligosaccharide chain:

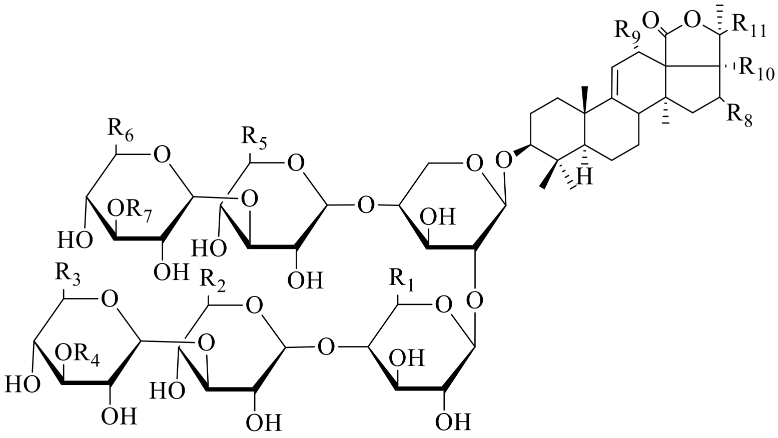
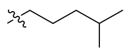
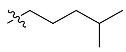
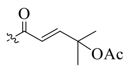
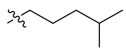
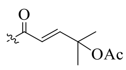
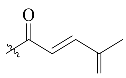
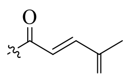
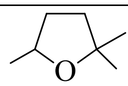
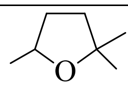
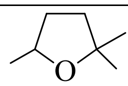


Table 6: Holostane glycosides contain 3β-hydroxyholost-9(11)-ene with 6 sugar units oligosaccharide chain reported in genus *Holothuria*:

Species	Compound Name	R^{1}	R^{2}	R^{3}	R^{4}	R^{5}	R^{6}	R^{7}	R^{8}	R^{9}	R^{10}	R^{11}	Ref
H. lessoni	Lessonioside A	CH_3	H	CH_2OH	CH_3	CH_2OH	CH_2OH	CH_3	OAc	OH	OH		**(Bahrami and Franco, 2015)**
H. lessoni	Lessonioside B	CH_3	CH_2OH	CH_3	H	CH_2OH	CH_2OH	CH_3	OAc	OH	OH		**(Bahrami and Franco, 2015)**
H. lessoni	Lessonioside C	CH_2-OH	H	CH_2OH	CH_3	H	H	CH_3	=O	OH	OH		**(Bahrami and Franco, 2015)**
H. essoni	Lessonioside D	CH_3	CH_2OH	H	CH_3	CH_2OH	CH_2OH	CH_3	OAc	OH	OH		**(Bahrami and Franco, 2015)**
H. lessoni	Lessonioside E	CH_3	CH_2OH	CH_2OH	H	H	H	CH_3	=O	OH	OH		**(Bahrami and Franco, 2015)**
H. essoni	Lessonioside F	CH_3	CH_2OH	CH_2OH	H	CH_2OH	CH_2OH	CH_3	=O	OH	OH		**(Bahrami and Franco, 2015)**
H. lessoni	Lessonioside G	CH_2-OH	H	CH_2OH	CH_3	CH_2OH	CH_2OH	CH_3	=O	OH	OH		**(Bahrami and Franco, 2015)**
H. forskali	Holothurinoside s F_1	CH_2-OH	CH_2OH	CH_2OH	CH_3	CH_2OH	CH_3	H	H	H	H		**(Honey-Escandón *et al.*, 2015)**
H. forskali	Holothurinoside s G_1	CH_2-OH	CH_2OH	CH_2OH	CH_3	CH_2OH	CH_3	H	H	OH	H		**(Honey-Escandón *et al.*, 2015)**
H. forskali	Holothurinoside s G	CH_3	CH_2OH	CH_2OH	CH_3	CH_2OH	CH_3	H	H	OH	OH		**(Honey-Escandón *et al.*, 2015)**

2.2.2- Holostane glycosides contain 3β-hydroxyholost-8(9)-ene:

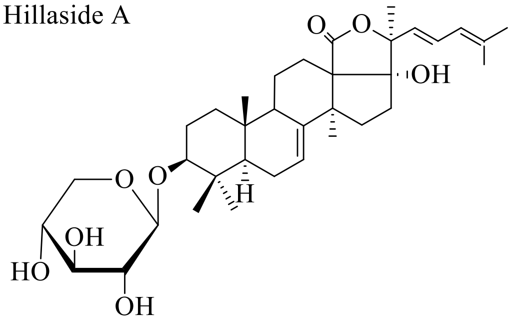
- Until now there is no triterpene glycosides with 3β-hydroxyholost-8(9)-ene isolated from *Holothuria* genus.

2.2.3. -Holostane glycosides contain 3β-hydroxyholost-7(8)-ene:

2.2.3.1- Holostane glycosides contain 3β-hydroxyholost-7(8)-ene with 1-3 sugar units oligosaccharide chain:

Hillaside A is a triterpene glycoside with a monosaccharide chain which was isolated from *Holothuria hilla* sea cucumber, its structure was deduced with spectral data and chemical analysis (**Wu *et al.*, 2007**).

Hillaside A



- **Holostane glycosides contain 3*β*-hydroxyholost-7(8)-ene with 4 sugar units oligosaccharide chain:**

Until now there is no triterpene glycosides with 3β-hydroxyholost-7(8)-ene with 4 sugar units isolated from *Holothuria* genus.

- **Holostane glycosides contain 3β-hydroxyholost-7(8)-ene with 5 sugar units oligosaccharide chain:**

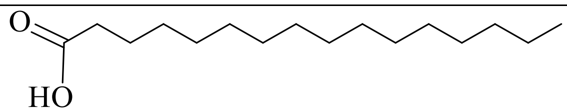
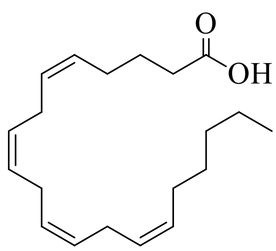
Up to now there is no triterpene glycosides with 3β-hydroxyholost-7(8)-ene with 5 sugar units isolated from *Holothuria* genus.

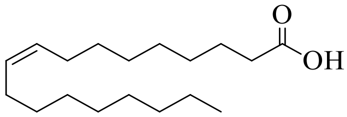
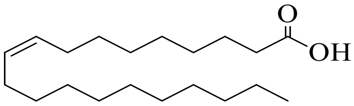
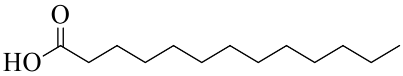
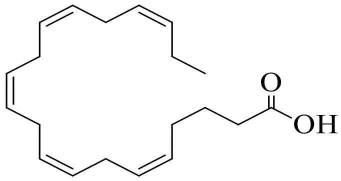
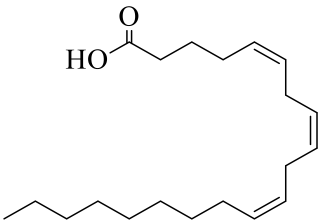
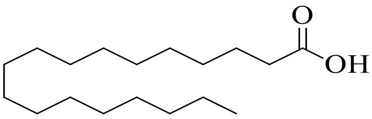
- **Holostane glycosides contain 3β-hydroxyholost-7(8)-ene with 6 sugar units oligosaccharide chain:**

Up till now there is no triterpene glycosides with 3β-hydroxyholost-7(8)-ene with 6 sugar units isolated from *Holothuria* genus.

2.3: Fatty acids: Several fatty acids have been identified in genus *Holothuria* (Table 7)

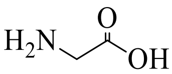
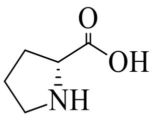
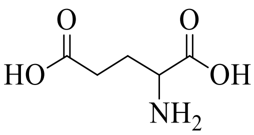
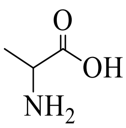
Table 7: Fatty acids reported in genus *Holothuria*

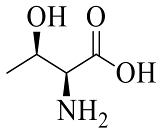
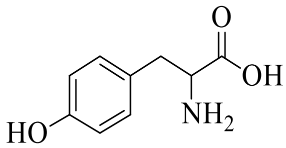
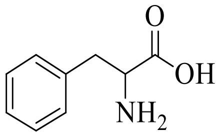
Species	Compound Name	Compound Structure	Reference
H. Leucospilota *H. sacbra*	Palmitic acid		**(Ceesay *et al.*, 2019)** (**Yahyavi *et al.*, 2012**)
H. Leucospilota *H. Sacbra* *H. tubulosa,* *H. mammata* *H. polii*	Arachidonic acid		(**Yahyavi *et al.*, 2012**) **(Mercedes *et al.*, 2018).**

H. leucospilota	Oleic acid		(**Yahyavi *et al.*, 2012**)
H. sacbra	Gadoleic acid		(**Yahyavi *et al.*, 2012**)
H.scabra, *H. leucospilota*, *H. atra*	Myristic acid		(**Ridzwan *et al.*, 2014**)
H. fuscogilva *H. mammata*	Eicosapentaenoic acid		**(Fawzya *et al.*, 2015)** (**Santos *et al.*, 2017**)
H. fuscogilva	Eicosatrienoic acid		**(Fawzya *et al.*, 2015)**
H. mammata	Stearic acid		(**Santos *et al.*, 2017**)

2.4: Amino acids: Numerous amino acids have been reported in genus *Holothuria* (Table 8)

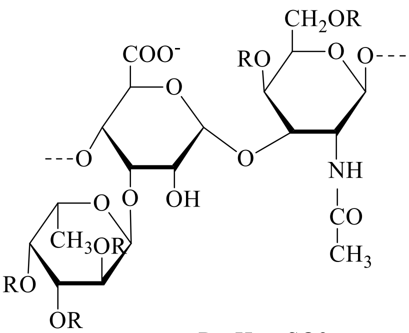
Table 8: Amino acids reported in genus *Holothuria*.

Species	Compound Name	Compound Structure	Reference
H. scabra	Glycine		(**Sroyraya *et al.*, 2017**)
H. scabra	Proline		(**Sroyraya *et al.*, 2017**)
H. scabra	Glutamic		(**Sroyraya *et al.*, 2017**)
H. scabra	Alanine		**(Ridwanudin *et al.*, 2018)**

H. fuscopunctata, *H. fuscogilva*	Threonine		(**Wen** ***et al.***, **2010**)
H. fuscopunctata, *H. fuscogilva*	Tyrosine		(**Wen** ***et al.***, **2010**)
H. fuscopunctata, *H. fuscogilva*	Phenylalanine		(**Wen** ***et al.***, **2010**)

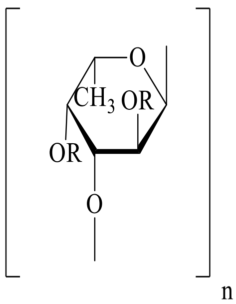
2.5 : Polysaccharides

- There are two types of sea cucumber polysaccharides have been isolated fucosylated chondroitin sulfate (FuCS) and fucan sulfates which usually called fucoidans. The fucoidans structure is usually made from linear or branched (α1→3)- and/or (α1→4)-linked fucosyl backbones with sulfate group substitute at C-2 and/or C-4.Fucoidans structures usually differ according to using different extraction procedures and different species so they may differ in monosaccharide composition, different linkages modes, molecular masses and sulfation patterns (**Mansour** ***et al.*****, 2019**).
- Neutral glycans can be considered the third type of sea cucumber polysaccharides but it was only isolated from *Holothuria edulis* species (**Luo** ***et al.*****, 2013**).
- Fucosylated chondroitin sulfate (FuCS) and sulfated fucan polysaccharides were isolated from *Holothuria nobilis* and *Holothuria edulis*,The FuCSs showed higher anticoagulant activity than the sulfated fucans, despite of the fact that the FuCSs molecular sizes are smaller than the sulfated fucans polysaccharides (**Santos** ***et al.*****, 2017**).

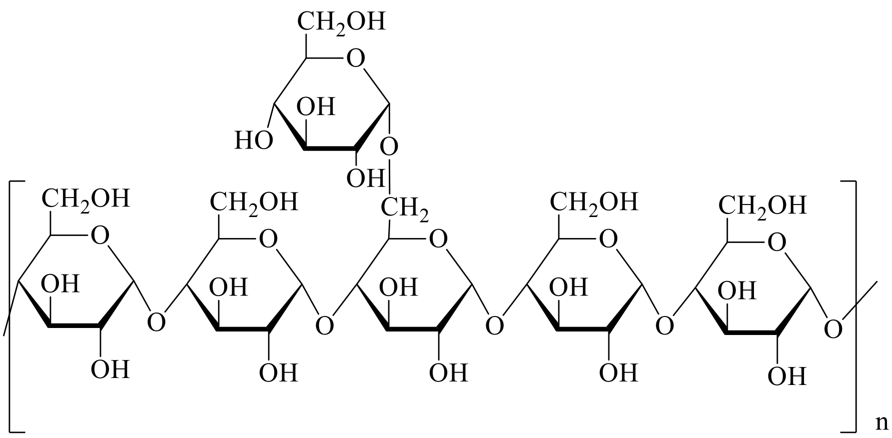


R= H or SO3

Fucosylated chondroitin sulfate
FuCS preponderant structure



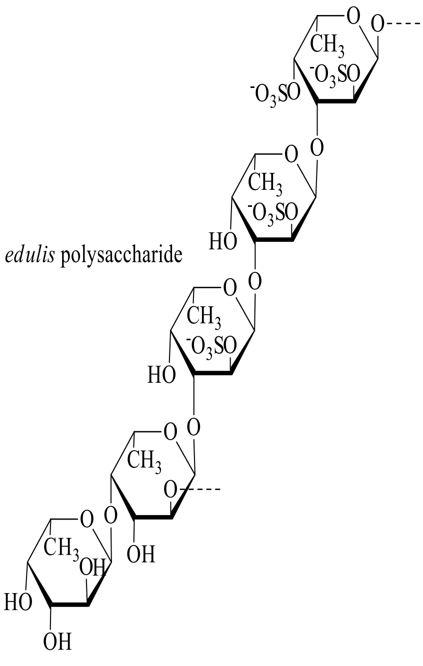
Basic backbone of 1-3-linked fucose polysaccharide in most sulfated fucans in sea cucumbers. R may be H, SO_3, or a fucose or galactose side chain.



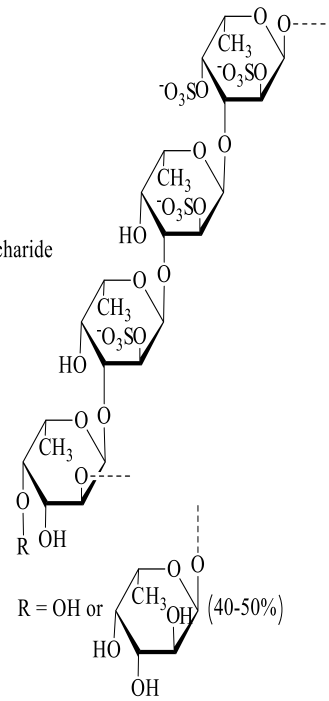
Holothuria edulis neutral glucan
The main residue of polysaccharide is an alpha-(1-4)-D-glucan branched with a single alpa-D-glucose at C-6 every five residues on average

- Two sulfated fucans were isolated from *Ludwigothurea grisea* (*Holothuria grisea*) and *Holothuria edulis* sea cucumbers and their structures were illustrated by the combination of NMR spectroscopy, chemical analysis, methylation experiments and specific optical rotation. The two sulfated *α*-L-fucans are linear polysaccharides which consist of a repeated tetrasaccharide backbone unit characterized by O-sulfation pattern with an unsulfated side chain fucose unit. All *H. edulis α*-L-fucan polysaccharides are fucosylated at position O-4 of the tetrasaccharide repeated unit but the *L.grisea* sulfated fucans are not all fucosylated at 4-position, only 40-50% are fucosylated at the backbone (**Wu** ***et al***., **2015**).

Holothuria edulis polysaccharide

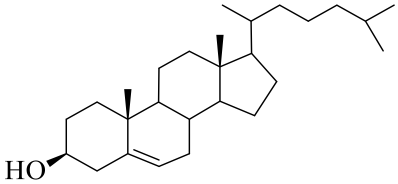
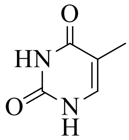
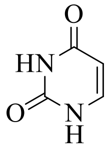
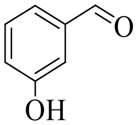
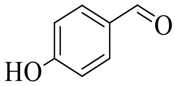
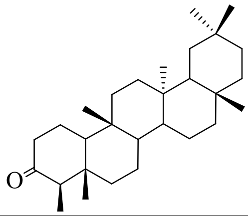
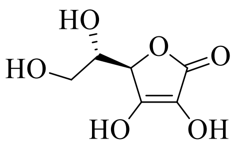
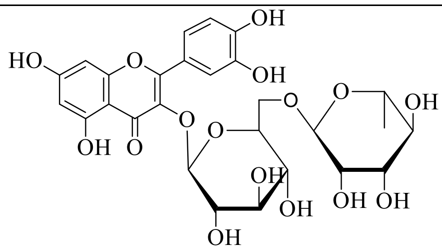
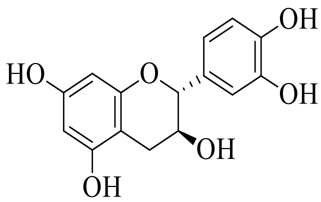


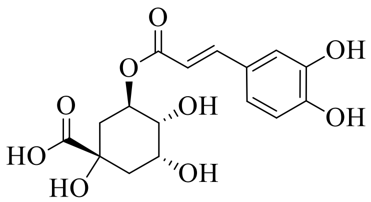
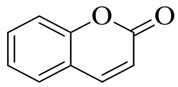
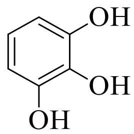
Holothuria grisea polysaccharide



2.6: Miscellaneous compounds:

Table 9: Miscellaneous compounds reported in genus *Holothuria*.

Species	Compound Name	Compound Structure	Reference
H. nobilis	Cholesterol		(**Zhang *et al*.**, **2008**)
H. nobilis	Thymine		(**Zhang *et al*.**, **2008**)
H. nobilis	Uracil		(**Zhang *et al*.**, **2008**)
H. scabra	3-Hydroxybenzaldehyde		(**Nobsathian *et al*.**, **2017**)
H. scabra	4-Hydroxybenzaldehyde		(**Nobsathian *et al*.**, **2017**)
H. scabra	Friedelin		(**Nobsathian *et al*.**, **2017**)
H. atra	Ascorbic acid		**(Esmat *et al*., 2013)**
H. atra	Rutin		**(Esmat *et al*., 2013)**
H. atra	Catechin		**(Esmat *et al*., 2013)**

H. atra	Chlorogenic acid		**(Esmat *et al.*, 2013)**
H. atra	Coumaric acid		**(Esmat *et al.*, 2013)**
H. atra	Pyrogallol		**(Esmat *et al.*, 2013)**

3. Conclusion:

In this review we covered comprehensively the phytochemicals reported in sea cucumbers belonging to genus *Holothuria*. Our study revealed that this genus of sea cucumber is a precious source of chemically different natural products, especially cerebrosides, saponins, and fatty acids.

References:

Ahmed, M.I., Aamer, M.A., Lawrence, A.J. 2016. Identification of the Holothurian species of the Red Sea and Gulf of Aqaba using DNA barcoding technique. Egyptian Journal of Aquatic Biology and Fisheries. 20, 1-7. 10.21608/ejabf.2016.11127.

Bahrami, Y., Zhang, W., Chataway, T., Franco, C. 2014. Structural elucidation of novel saponins in the sea cucumber *Holothuria lessoni*. Marine Drugs, 12, 4439-4473.

Bahrami, Y. and Franco, C. M. M. 2015. Structure elucidation of new acetylated saponins, lessoniosides A, B, C, D, and E, and non-acetylated saponins, lessoniosides F and G from the viscera of the sea cucumber *Holothuria lessoni*. Marine Drugs, 13, 597-617.

Bordbar, S., Anwar, F., Saari, N. 2011. High-Value components and bioactives from sea cucumbers for functional foods - A Review. Marine Drugs, 9, 1761-1805.

Caulier, G., Dyck, S. V., Gerbaux, P., Eeckhaut, I., Flammang, P. 2011. Review of saponin diversity in sea cucumbers belonging to the family *Holothuriidae.* Beche-de-Mer Information. Bulletin, 31, 48-54.

Caulier, G., Mezali, K., Soualili, D., Decroo, C., Demeyer, M., Eeckhaut, I., Gerbaux, P., Flammang, P. 2016. Chemical characterization of saponins contained in the body wall and the Cuvierian tubules of the sea cucumber *Holothuria* (Platyperona) *sanctori* (Delle Chiaje, 1823). Biochemical Systemic and Ecology, 68, 119-127.

Ceesay, A., Shamsudin, M. N., Alipiah, N. M., Ismail, I. S. 2012. Biodiversity and Adaptability of *Holothuria leucospilota* and *Stichopus japonicus* sea cucumber species in artificial environment. Journal of Aquaculture Research & Development, 3, 123.

Ceesay, A., Shamsudin, M. N., Aliyu-Paiko, M., Ismail, I. S., Nazarudin, M. F., Alipiah, N. M. 2019. Extraction and Characterization of Organ Components of the Malaysian Sea Cucumber *Holothuria leucospilota* Yielded Bioactives Exhibiting Diverse Properties. Biomed Reseach International, 19, 1-16.

Dang, N. H., Thanh, N. V., Kiem, P. V., Huong, L. M., Minh, C. V., Kim, Y. H. 2007. Two new triterpene glycosides from the Vietnamese sea cucumber *Holothuria scabra*. Archives of Pharmacal Research, 30, 1387-1391.

Elyakov, G. B., Stonic, V. A., Levina, E. V., Slanke, V. P., Kuznetsova, T. A. 1973. Glycosides of marine invertebrates-I. A comparative study of the glycosides fraction of Pacific sea cucumbers. Comparative Biochemistry and Physiology, 44, 325-336.

Elyakov, G. B., Kuznetsova, T. A., Stonic, V. A., Levin, V. S., Albores, R. 1975. Glycosides of marine invertebrates-IV. A comparative study of the glycosides from Cuban sublittoral holothurians. Comparative Biochemistry and Physiology, 52, 413-417.

Esmat, A. Y., Said, M. M., Soliman, A. A., EL-masry, K. S., Badiea, E. A. 2013. Bioactive compounds, antioxidant potential, and hepatoprotective activity of sea cucumber (*Holothuria atra*) against thioacetamide intoxication in rats. Nutrition, 29, 258-267.

Fawzya, Y., Januar, H., Susilowati, R., Chasanah, E. 2015. Chemical composition and fatty acid profile of some Indonesian sea cucumbers. Squalen Bulletin of Marine and Fisheries Postharvest and Biotechnology, 10, 27-34.

Grabley, S. and Sattler, I. 2003. Natural products for lead identification: nature is a valuable resource for proving tools. In: A, Hillisch., R, Hilgenfeld., eds. Modern Methods of Drug Discovery. Birkhäuser, Basel: Springer, 87-107.

Haefner, B. 2003. Drugs from the deep: marine natural products as drug candidates. Drug Discovery Today, 8, 536-544.

Han, H., Yi, Y. H., Liu, B. S., Wang, X. H., Pan, M. X. 2008. Leucospilotaside C, a new sulfated triterpene glycoside from sea cucumber *Holothuria leucospilota*. Chinese Chemical Letters, 19, 1462-1464.

Han, H., Yi, Y., Xu, Q., La, M., Zhang, H. 2009. Two new cytotoxic triterpene glycosides from the sea cucumber *Holothuria scabra*. Planta Medica, 75, 1608–1612

Han, H., Li, l., Yi, Y.-H., Wang, X.-H., Pan, M.-X. 2012. Triterpene glycosides from sea cucumber *Holothuria scabra* with cytotoxic activity. Chin. Herb. Med, 4, 183-188.

Honey-Escandón, M., Arreguín-Espinosa, R., Solís-Marín, F.A., Samyn, Y. 2015. Biological and taxonomic perspective of triterpenoid glycosides of sea cucumbers of the family Holothuriidae (Echinodermata, Holothuroidea). Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology, 180, 16-39.

https://doi.org/10.1016/j.cbpb.2014.09.007
http://www.marinespecies.org/

Hua, H., Yi, Y.-H., Li, L., Liu, B.-S., Pan, M.-X., Yan, B., Wang, X.-H. 2009. Triterpene glycosides from sea cucumber *Holothuria leucospilota*. Chinise Journal of Natural Medicines, 7, 346-350.

Hue, N., Montagnac, A., Pais, M., Serani, L., Laprevote, O. 2001. Structural elucidation of eighteen cerebrosides from *Holothuria coronopertusa* in a complex mixture by high-energy collsion-induced dissociation of $[M+Li]^+$ ions. European Journal of Mass Spectrometry, 7, 409-417.

Kitagwa, I., Nishino, T., Matsuno, T., Akutsu, H., Kyogoku, Y. 1978. Structure of holothurine B, a pharmacologically active triterpene-oligoglycoside from the sea cucumber *Holothuria leucospilota* Brandt. Tetrahedron Letters, 11, 985-988.

Kitagwa, I., Nishino, T., Kyogoku, Y. 1979. Structure of holothurine A, a biologically active triterpene-oligoglycoside from the sea cucumber. *Holothuria leucospilota* Brandt. Tetrahedron Letters, 20, 1419-1422.

Kitagawa, I., Kobayashi, M., Son, B.W., Siuzukia, S., Kyogokub, Y. 1989. Marine natural products,XIX pervicosides A, B, and C, lanostane-type triterpene-oligoglycoside sulfates from the sea cucumber *Holothuria pervicax*. Chemical and pharmaceutical bulletin, 37, 1230–1234.

Kobayashi, M., Hori, M., Kan, K., Yasuzawa, T., Matsui, M., Suzuki, S., Kitagawa, I. 1991. Marine natural product .XXVII. Distribution of lanostane-type triterpene oligoglycosides in ten kinds of Okinawan sea cucumbers. Chemical and pharmaceutical bulletin, 39, 2282-2287.

Lalli, C. M and Parson T. R. 1993. Biological Oceanography. New York, Butterworth-Heinemann. Elsevier, 1-10.

Luo, L., Wu, M., Xu, L., Lian, W., Xiang, J., Lu, F., Gao, N., Xiao, C., Wang, S., Zhao, J. 2013. Comparison of physicochemical characteristics and anticoagulant activities of polysaccharides from three sea cucumbers. Marine Drugs, 11, 399–417.

Mansour, M. B., Balti, R., Yacoubi, L., Ollivier, V., Chaubet, F., Maaroufi, R. M. 2019. Primary structure and anticoagulant activity of fucoidan from the sea cucumber *Holothuria polii*. International Journal of Biological. Macromolecules, 121, 1145-1153.

Mercedes, G. W., Roggatz, C. C., Rodrigues, M. J., Barreira, L., Silva, M. M., Custódio, L. 2018. A new insight into the influence of habitat on the biochemical properties of three commercial sea cucumber species. International Aquatic Research, 10, 361-373.

Mohammed, I. A. 2016. Separation of a novel species from Actinopyga mauritiana (Holothuroidea: Holothuriidae) species complex, based on ecological, morphological and mitochondrial DNA evidence. Egypt. Egyptian Journal of Aquatic Biology and Fisheries, 20, 39-45.

Mondol, M. A., Shin, H. J., Rahman, M. A., Islam, M. T. 2017. Sea cucumber glycosides: Chemical structures, producing species, and important biological properties. Marine Drugs, 15, 1-35.

Nobsathian, S., Tuchinda, P., Sobhon , P., Tinikul, Y., Poljaroen, J., Tinikul, R., Sroyraya, M., Poomton, T., Chaichotranunt, S. 2017. An antioxidant activity of the whole body of *Holothuria scabra*. Chemical and Biological Technologies in Agriculture, 4, 1-5.

O'loughlin, P. M., Paulay, G., Vandenspiegel, D., Samyn, Y. 2007. New Holothuria species from Australia (Echinodermata: Holothuroidea: Holothuriidae), with comments on the origin of deep and cool holothuriids. Memoirs of Museum Victoria, 64, 35-52.

Ridwanudin, A., Indriana, L., Kunzmann, A. 2018. No difference in nutritional profiles of wild and cultured juvenile sandfish, *Holothuria scabra*. Annual Research & Review in Biology, 26, 1-11.

Ridzwan, B.H., Hanita, M.H., Nurzafirah, M., Siti Norshuhadaa, M. P., Farah Hanis, Z. 2014. Free Fatty Acids Composition in Lipid Extracts of Several Sea Cucumbers Species from Malaysia. International Journal of Bioscience, Biochemistry and Bioinformatics, 4, 204-207.

Rodriguez, J., Castro, R., Riguera, R. 1991. Holothurinosides: New antitumour non sulphated triterpenoid glycosides from the sea cucumber *Holothuria forskalii*, Tetrahedron, 47, 4753-4762.

Santos, R., Dias, S., Tecelão, C., Pedrosa, R., Pombo, A. 2017. Reproductive biological characteristics and fatty acid profile of *Holothuria mammata*. SPC Beche-de-mer Information Bulletin, 37, 57-64.

Silchenko, A. S., Stonik, V. A., Avilon, S. A., Kalinin, V. I., Kalinovsky, A. I., Zaharenko, A. M., Smirnov, A. V., Mollo, E., Cimino, G. 2005. Holothurins B_2, B_3 and B_4, new triterpene glycosides from Mediterranean sea cucumbers of the genus *Holothuria*. Journal of Natural Products, 68, 564-567.

Sroyraya, M., Hanna, P. J., Siangcham, T., Tinikul, R., Jattujan, P., Poomtong, T., Sobhon, P. 2017. Nutritional components of the sea cucumber *Holothuria scabra*. Functional Foods in Health and Disease, 7, 168-181.

Stonik, V.A. 1986. Some terpenoid and steroid derivatives from echinoderms and sponges. Pure and Applied Chemistry, 58, 423-436.

Sun, G.-Q., Li, L., Yi, Y.-H., Yuan, W.-H., Liu, B.-S., Weng, Y.-Y., Zhang, S.-L., Sun, P., Wang, Z.-L. 2008. Two new cytotoxic nonsulfated pentasaccharide holostane (=20-hydroxylanostan-18-oic acid gamma-lactone) glycosides from the sea cucumber *Holothuria grisea*. Helvetica Chimica Acta, 9, 1453–1460.

Wen, J., Hu, C., Fan, S. 2010. Chemical composition and nutritional quality of sea cucumbers. Journal of the Science of Food and Agriculture, 90, 2469-2474.

Wu, J., Yi, Y. H., Tang, H. F., Wu, H. M., Zou, Z. R., Lin, H. W. 2006a. Nobilisides A - C, Three New Triterpene Glycosides from the Sea Cucumber *Holothuria nobilis*. Planta Medica, 72, 932-935.

Wu, J., Yi, Y. H., Tang, H.F., Zou, Z. R.,Wu, H. M. 2006b. Structure and cytotoxicity of a new lanostane-type triterpene glycoside from the sea cucumber *Holothuria hilla*. Chemistry & Biodiversity, 3, 1249-1254.

Wu, J., Yi, Y. H., Tang, H. F.,Wu, H. M., Zhou, Z. R. 2007. Hillasides A and B, two new cytotoxic triterpene glycosides from the sea cucumber *Holothuria hilla* Lesson. Journal of Asian Natural Products Research, 9, 609-615.

Wu, M., Xu, L., Zhao, L., Xiao, C., Geo, N., Luo, L., Yang, L., Li, Z., Chen, L., Zhao, J. 2015. Structural analysis and anticoagulant Activities of the novel sulfated fucan possessing a regular well-defined repeating unit from sea cucumber. Marine Drugs, 13, 2063-2084.

Yahyavi, M., Afkhami, M., Javadi, A., Ehsanpour, M., Khazaali, A., Koshnood, R., Mokhlesi, A. 2012. Fatty acid composition in two sea cucumber species *Holothuria scabra* and *Holothuria leucospilata* from Qeshm island (Persian Gulf). African Journal of Biotechnology, 11, 2862-2868.

Yamada, K., Harada, Y., Nagaregawa, Y., Miyamoto, T., Isobe, R., Higuchi, R. 1998. Isolation and structure of biologically active gangliosides from the sea cucumber *Holothuria pervicax*. Journal of Organic Chemistry, 48, 2519-2525.

Yamada, K., Harada, Y., Miyamoto, T., Isobe, R., Higuchi, R. 2000. Constituents of *Holothuroidea*.9. Isolation and structure of a new ganglioside molecular species from the sea cucumber *Holothuria pervicax*. Chemical and Pharmaceutical Bulletin, 48, 157-159.

Yamada, K., Matsubara, R., Kaneko, M., Miyamoto, T., Higuchi, R. 2001. Isolation and structure of a biologically active ganglioside molecular species from the sea cucumber *Holothuria leucospilota.* Chemical and Pharmaceutical Bulletin, 49, 447-452.

Yamada, K., Sasaki, K., Harada, Y., Isobe, R., Higuchi, R. 2002. Isolation and structure of glucocerebrosides from the sea cucumber *Holothuria pervicax.* Chemical and Pharmaceutical Bulletin, 50, 1467-1470.

Yamada, K., Onaka, H., Tanaka, M., Inaki, M., Higuchi, R. 2005. Determination of absolute configuration of the branched methyl group in ante-iso type side chain moiety on long chain base of glucocerebroside from the sea cucumber *Holothuria leucospilota*. Chemical and Pharmaceutical Bulletin, 53, 1333-1334.

Yasumoto, T., Nakamura, K., Hashimoto, Y. 1967. A new saponin holothurin B isolated from the sea cucumber *Holothuria vagabunda and Holothuria lubrica.* Agricultural and Biological Chemistry, 31, 7-10.

Yuan,W.H., Yi, Y. H., Tan, R. X.,Wang, Z. L., Sun, G. Q., Xue, M., Zhang, H. W., Tang, H. F. 2009. Antifungal triterpene glycosides from the sea cucumber *Holothuria* (*Microthele*) *axiloga*. Planta Medica, 75,647–653.

Zhang, S., Yi, Y. H., Tang, H. F. 2006. Bioactive triterpene glycosides from the sea cucumber *Holothuria fuscocinerea*. Journal of Natural Products, 69, 1492-1495.

Zhang, J. J., Dai, J. B., Chen, L. L., Ding, P. Y., WU, J. 2008. Chemical constituents from sea cucumber *Holothuria nobilis*. Journal of Chinese medicinal materials, 31, 538-539.