



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

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Abstract

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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

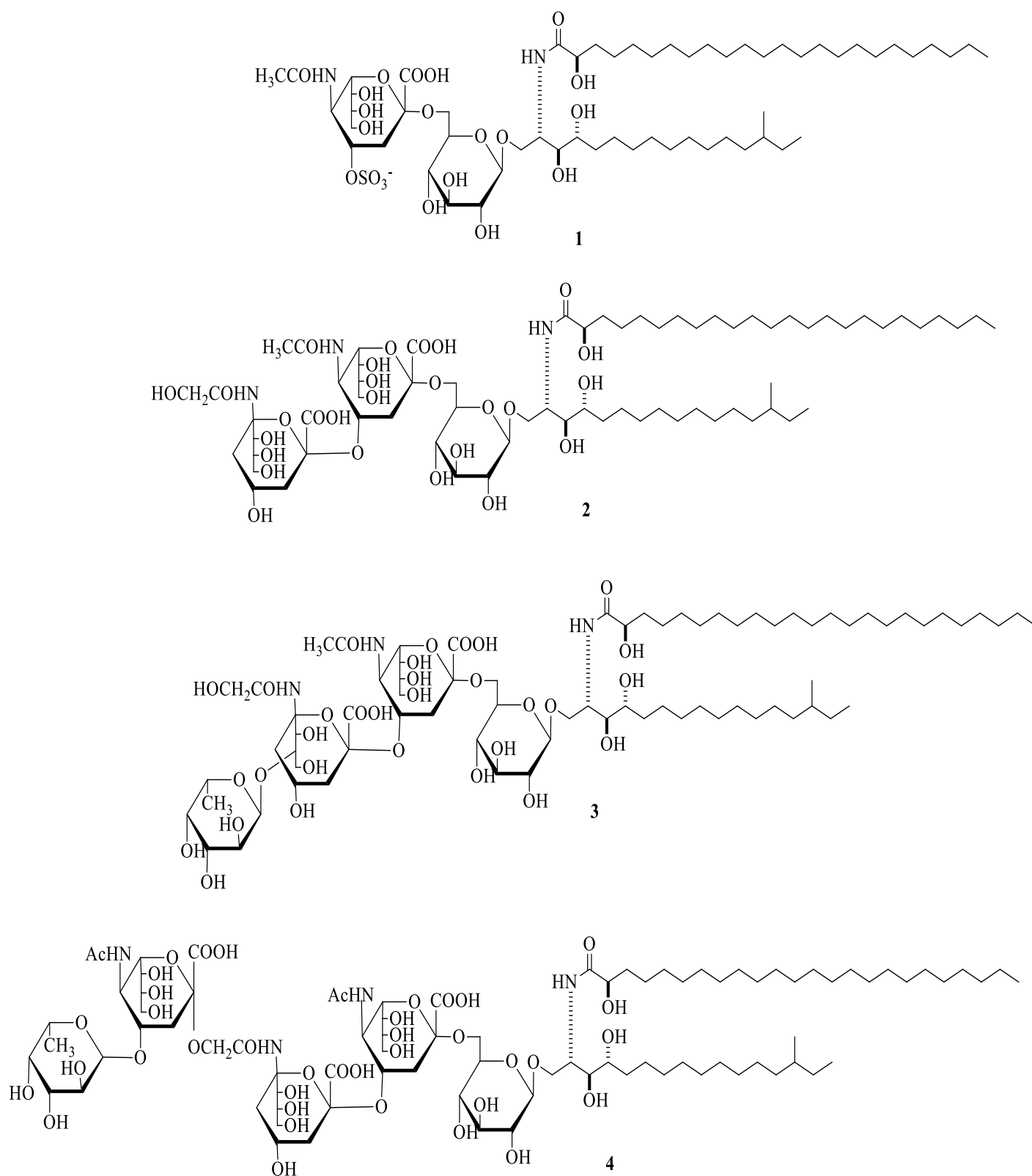
them, genus *Holothuria* which is the most predominant one according to the database in World Register of Marine Species (<http://www.marinespecies.org/>) and it is represented in Egypt by eight species (**Ahmed et al., 2016**). Phytochemical investigation of *Holothuria* sea cucumbers has led to the 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	<i>H. pervicax</i>	HPG-8	(Yamada et al., 1998).
2	<i>H. pervicax</i>	HPG-3	(Yamada et al., 1998).
3	<i>H. pervicax</i>	HPG-1	(Yamada et al., 1998).
4	<i>H. pervicax</i>	HPG-7	(Yamada et al., 2000)
5	<i>H. pervicax</i>	HPC-1	(Yamada et al., 2002)
6	<i>H. pervicax</i>	HPC-2	(Yamada et al., 2002)
7	<i>H. pervicax</i>	HPC-3-A and HPC-3-B	(Yamada et al., 2002)
8	<i>H. pervicax</i>	HPC-3-C - HPC-3-J	(Yamada et al., 2002)
9	<i>H. Leucospilota</i>	HLG-1	(Yamada et al., 2001)
10	<i>H. Leucospilota</i>	HLG-2	(Yamada et al., 2001)
11	<i>H. Leucospilota</i>	HLG-3	(Yamada et al., 2001)
12	<i>H. Leucospilota</i>	HLC-2-A	(Yamada et al., 2005)
13	<i>H. coronopertusa</i>	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)

**Figure 1: chemical structures of compounds 1-4**

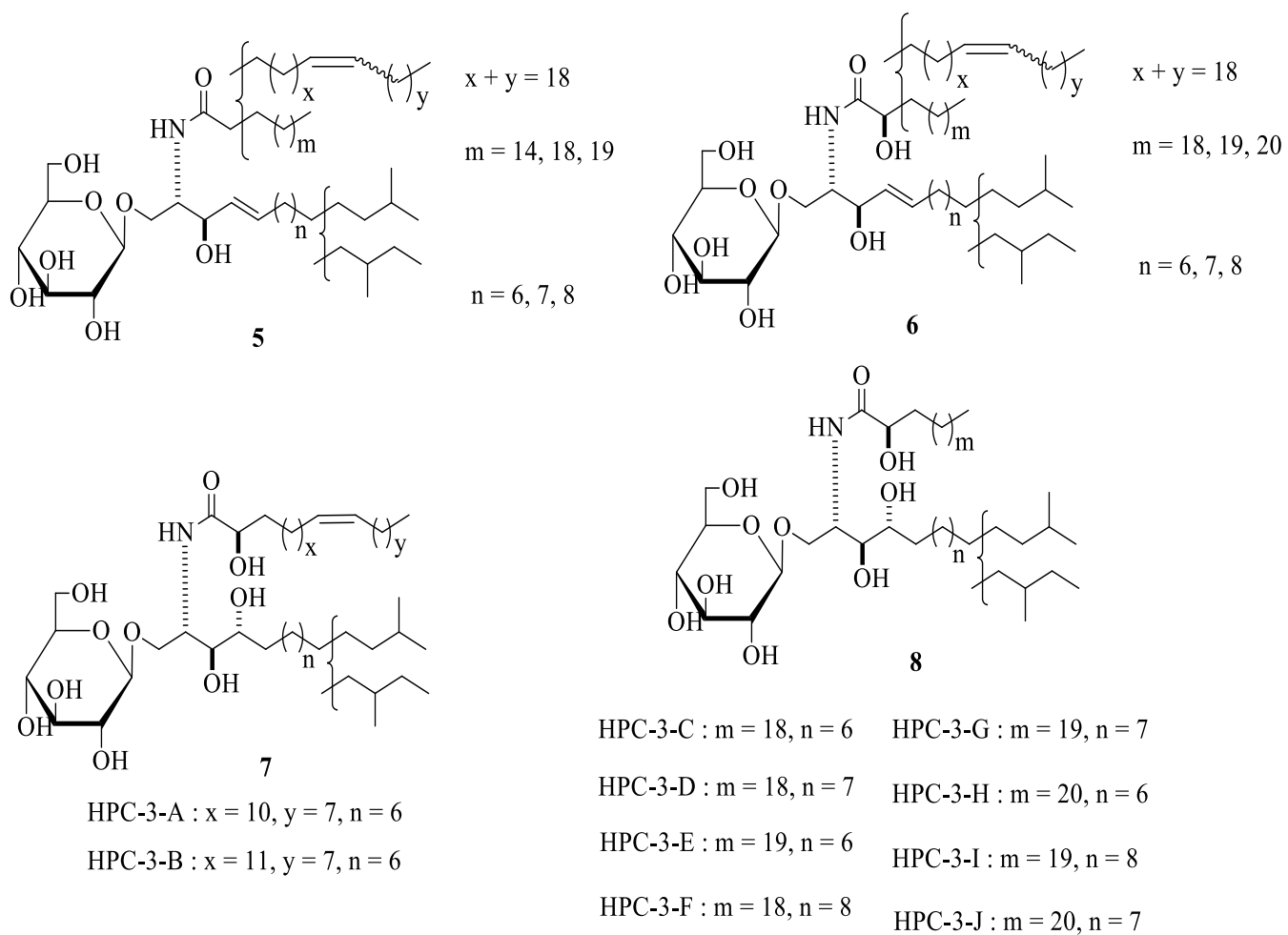


Figure 2: chemical structures of compounds 5-8.

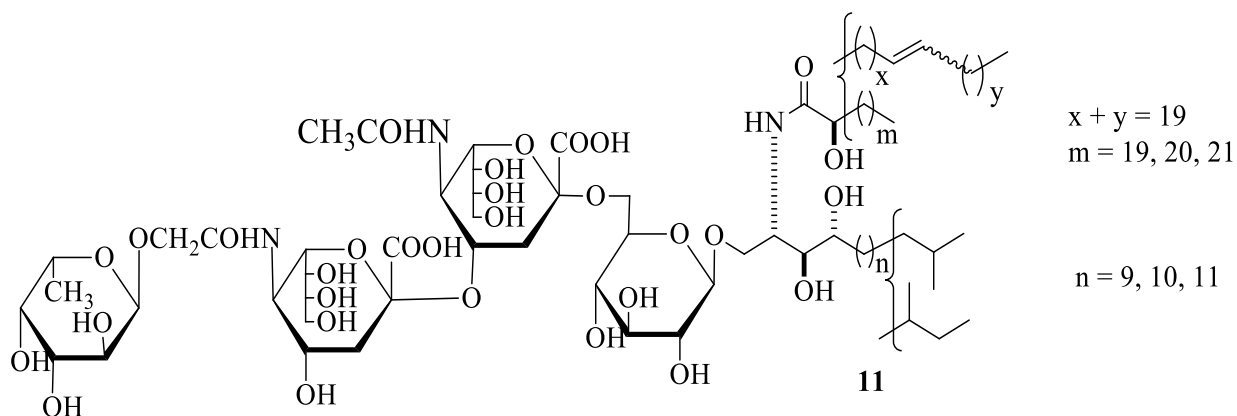
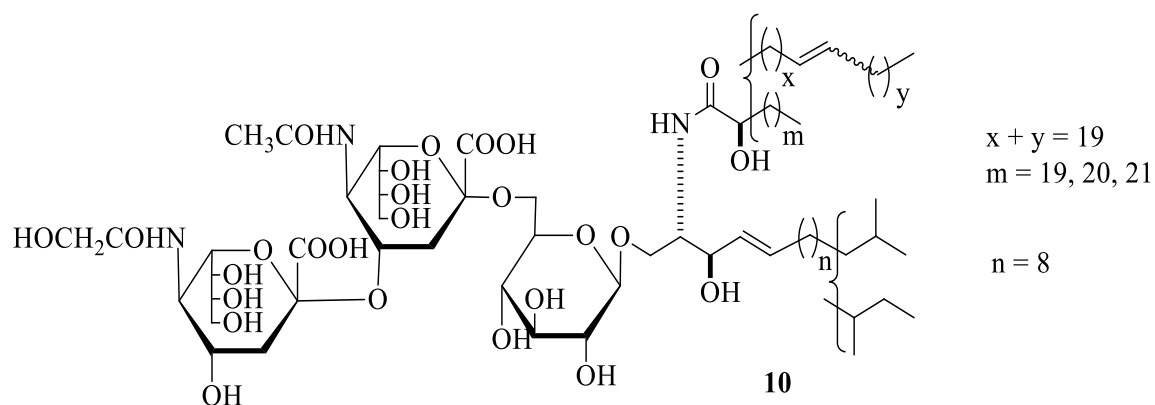
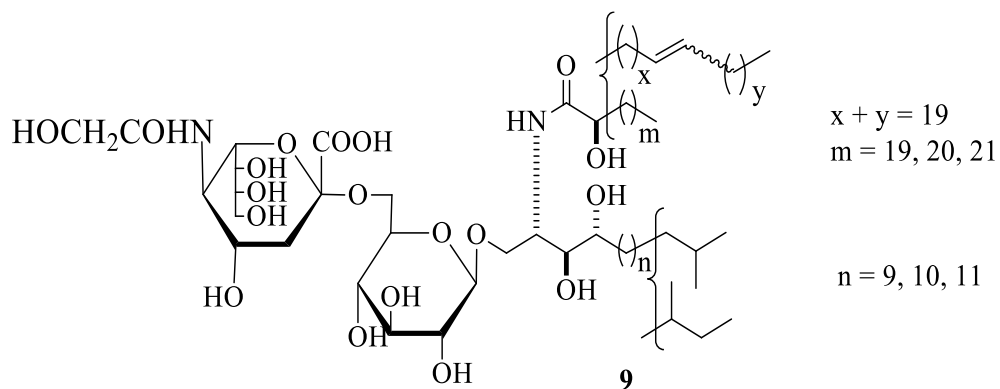
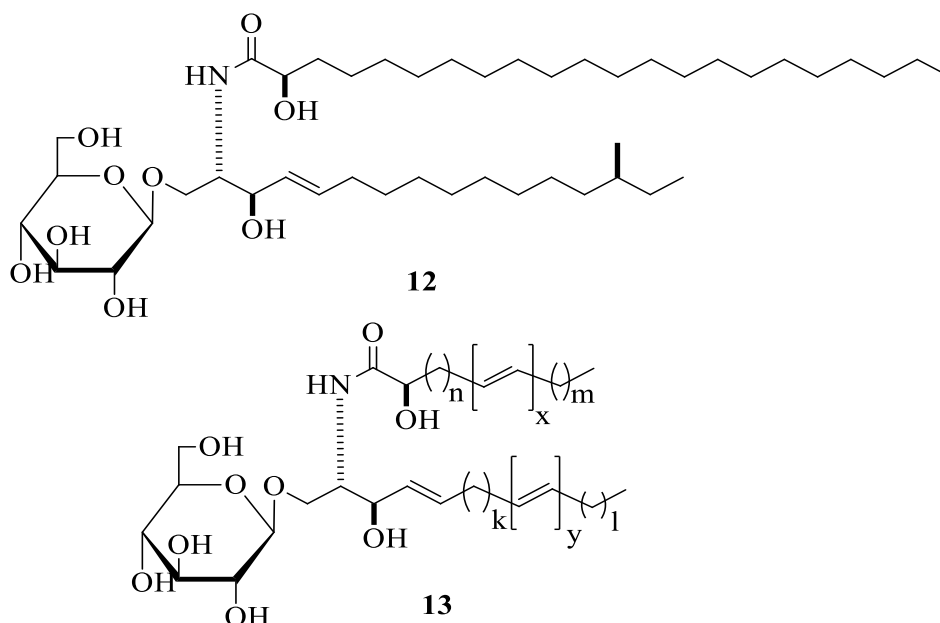


Figure 3: chemical structures of compounds 9-11.



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:

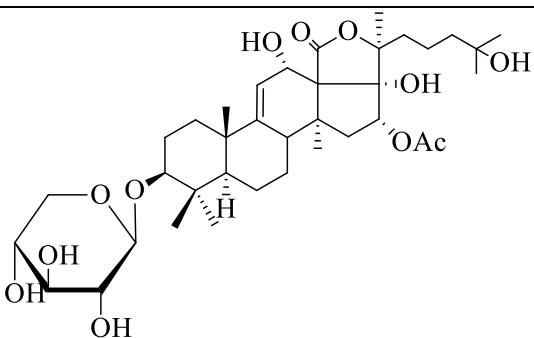
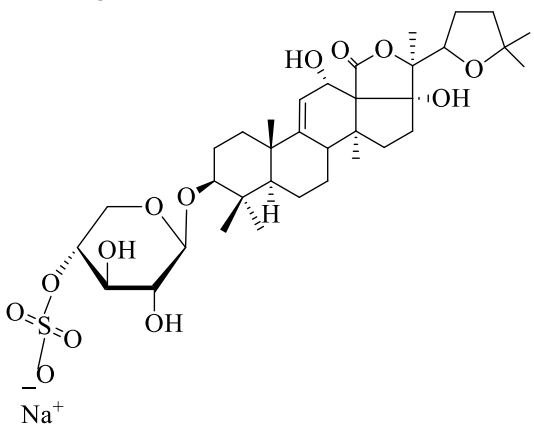
- Holostane glycosides contain 3β -hydroxyholost-9(11)-ene. See Tables (2,3,4,5 and 6)
- Holostane glycosides contain 3β -hydroxyholost-8(9)-ene.
- Holostane glycosides contain 3β -hydroxyholost-7(8)-ene.

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:

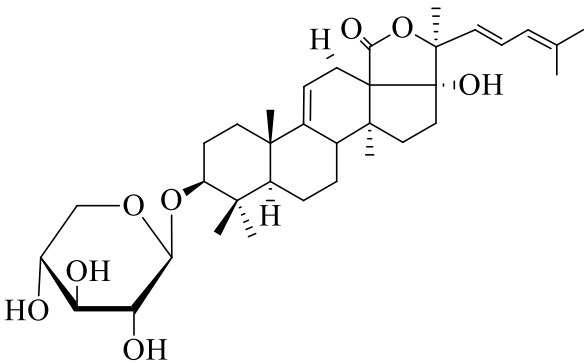
Table 2: Holostane glycosides contain 3β -hydroxyholost-9(11)-ene with 1-3 sugar units oligosaccharide chain reported in genus *Holothuria*:

Species	Compound Name	Compound Structure	Reference
<i>H. hilla</i>	Hillaside B		(Wu et al., 2007)
<i>H. leucospilota</i>	Leucospilotside C		(Han et al., 2008).

H. nobilis

Nobiliside A

(Wu *et al.*, 2006a)



H. nobilis

Nobiliside C

(Wu *et al.*, 2006a)

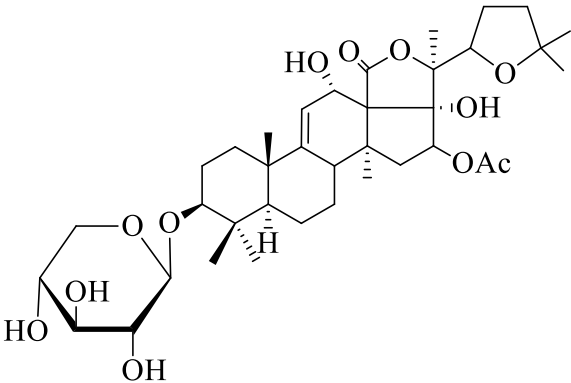
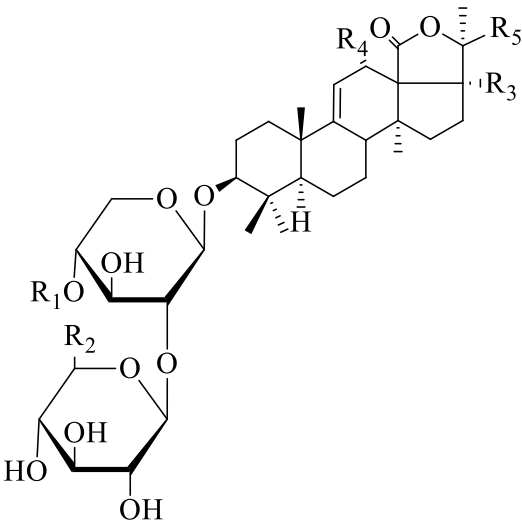
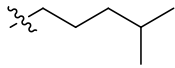
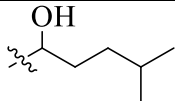
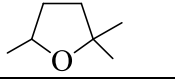
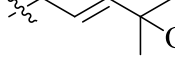
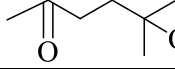
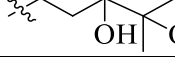
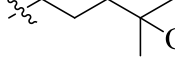
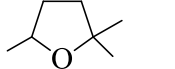
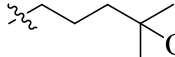
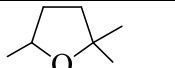


Table 3: Holostane glycosides contain 3 β -hydroxyholost-9(11)-ene with 1-3 sugar units oligosaccharide chain reported in geuns *Holothuria*:



Species	Compound Name	R ¹	R ²	R ³	R ⁴	R ⁵	Reference
<i>H. lubrica</i> , <i>H. arenicola</i> , <i>H. pervicax</i> , <i>H. nobilis</i> , <i>H. hilla</i> , <i>H. gracilis</i> , <i>H. difficilis</i> , <i>H. coluber</i> <i>H. pulla</i> , <i>H. cubana</i> ,	Holothurin B	SO ₃ Na	CH ₃	OH	OH		(Yasumoto <i>et al.</i> , 1967), (Elyakov <i>et al.</i> , 1973), (Elyakov <i>et al.</i> , 1975), (Kitagawa <i>et al.</i> , 1979),

<i>H.grisea</i> , <i>H. surinamensis</i> <i>H.mexicana</i> , <i>H.atra</i> <i>H.leucospilota</i> , <i>H.polii</i> , <i>H.axiloga</i> , <i>H.edulis</i> , <i>H.tubulosa</i> , <i>H. scabra</i> and <i>H. fuscocinerea</i>							(Kobayashi <i>et al.</i> ,1991), (Silchenko <i>et al.</i> , 2005), (Zhang <i>et al.</i> , 2006) (Dang <i>et al.</i> , 2007)
<i>H. leucospilota</i> , <i>H. atra</i>	Holothurin B ₁	SO ₃ Na	CH ₃	OH	OH		(Kitagawa <i>et al.</i> , 1978) (Kobayashi <i>et al.</i> , 1991)
<i>H. polii</i>	Holothurin B ₂	SO ₃ Na	CH ₃	OH	OH		(Silchenko <i>et al.</i> , 2005)
<i>H. polii</i>	Holothurin B ₃	SO ₃ Na	CH ₃	H	OH		(Silchenko <i>et al.</i> , 2005)
<i>H. polii</i>	Holothurin B ₄	SO ₃ Na	CH ₃	OH	OH		(Silchenko <i>et al.</i> , 2005)
<i>H. leucospilota</i>	leucospilotaside A	SO ₃ Na	CH ₃	OH	OH		(Hua <i>et al.</i> , 2009)
<i>H. leucospilota</i>	leucospilotaside B	SO ₃ Na	CH ₃	OH	OH		(Hua <i>et al.</i> , 2009)
<i>H. leucospilota</i>	leucospilotaside D	SO ₃ Na	CH ₃	OH	OH		(Honey-Escandón <i>et al.</i> , 2015)
<i>H. forskali</i>	Holothurinoside D	H	CH ₃	H	OH		(Rodriguez <i>et al.</i> , 1991)
<i>H. hilla</i>	Hillaside C	H	H	OH	OH		(Wu <i>et al.</i> , 2006b).
<i>H. nobilis</i>	Nobiliside B	SO ₃ Na	CH ₂ OH	OH	H		(Wu <i>et al.</i> , 2006a)

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

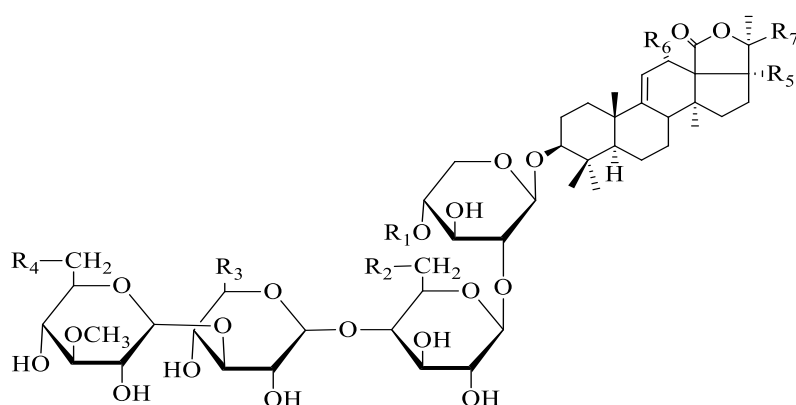
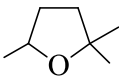
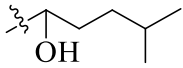
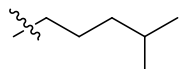
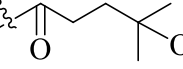
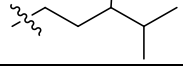
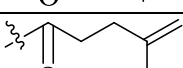
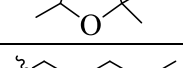
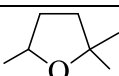
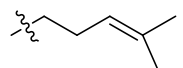
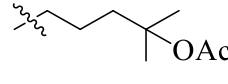
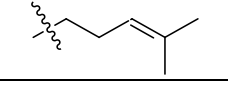
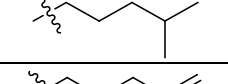
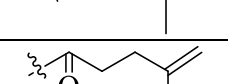
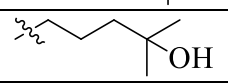
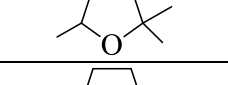
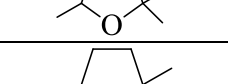
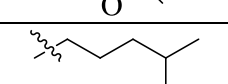
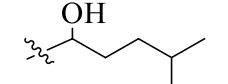
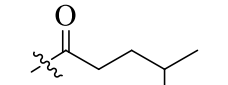
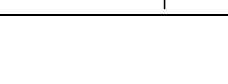
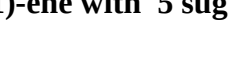


Table 4: Holostane glycosides contain 3 β -hydroxyholost-9(11)-ene with 4 sugar units oligosaccharide chain reported in genus *Holothuria*:

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

<i>H. pervicax</i>	Pervicosides A	SO ₃ Na	H	CH ₂ OH	OH	H	OH		(Kitagawa <i>et al.</i> , 1989)
<i>H. pervicax</i>	Pervicosides B	SO ₃ Na	H	CH ₂ OH	OH	H	OH		(Kitagawa <i>et al.</i> , 1989)
<i>H. pervicax</i>	Pervicosides C	SO ₃ Na	H	CH ₂ OH	OH	H	OH		(Kitagawa <i>et al.</i> , 1989)
<i>H. scabra</i>	Scabraside A	SO ₃ Na	H	CH ₂ OH	OH	OH	OH		(Han <i>et al.</i> , 2009).
<i>H. scabra</i>	Scabraside B	SO ₃ Na	H	CH ₂ OH	OH	OH	OH		(Han <i>et al.</i> , 2009).
<i>H. scabra</i>	Scabraside D	SO ₃ Na	H	CH ₂ OH	OH	OH	OH		(Han <i>et al.</i> , 2012).
<i>H. forskali</i>	Holothurinoside C	H	H	CH ₂ OH	OH	H	OH		(Rodriguez <i>et al.</i> , 1991).
<i>H. lesson</i>	Holothurinoside J1	H	OH	CH ₂ OH	OH	OH	OH		(Bahrami <i>et al.</i> , 2014)
<i>H. forskali</i>	Holothurinoside C1	H	OH	CH ₂ OH	OH	H	H		(Honey-Escandón <i>et al.</i> , 2015)
<i>H. lesson</i>	Holothurinoside Y	H	OH	CH ₃	OH	OH	OH		(Bahrami <i>et al.</i> , 2014)
<i>H. lesson</i>	Holothurinoside Z	H	OH	CH ₃	OH	OH	OH		(Bahrami <i>et al.</i> , 2014)
<i>H. lesson</i>	Holothurinoside X	H	OH	H	OH	OH	OH		(Bahrami <i>et al.</i> , 2014)

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

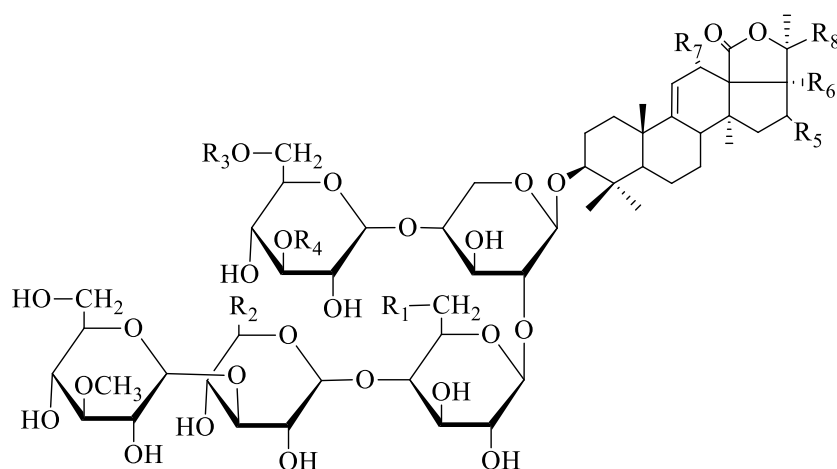
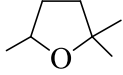
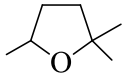
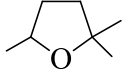
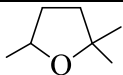
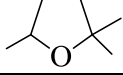
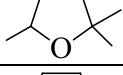
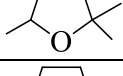
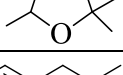
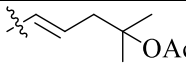
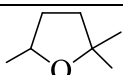
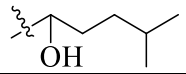
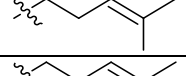
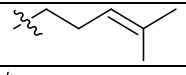
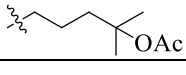


Table 5: Holostane glycosides contain 3 β -hydroxyholost-9(11)-ene with 5 sugar units oligosaccharide chain reported in genus *Holothuria*:

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

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

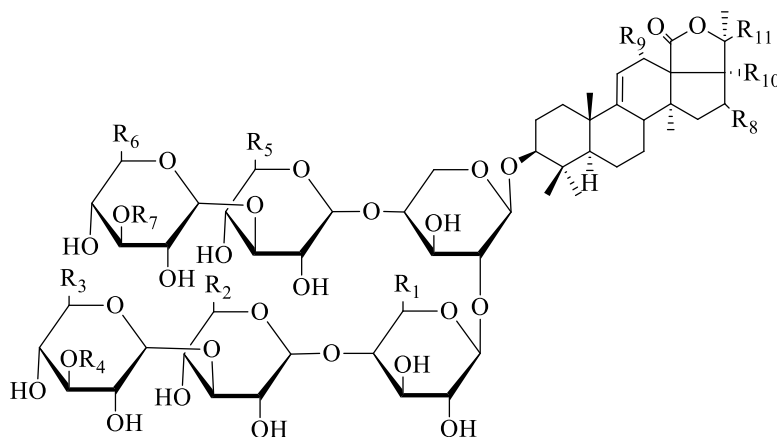


Table 6: Holostane glycosides contain 3 β -hydroxyholost-9(11)-ene with 6 sugar units oligosaccharide chain reported in genus *Holothuria*:

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
<i>H. lessoni</i>	Lessonioside A	CH ₃	H	CH ₂ OH	CH ₃	CH ₂ OH	CH ₂ OH	CH ₃	OAc	OH	OH		(Bahrami and Franco, 2015)
<i>H. lessoni</i>	Lessonioside B	CH ₃	CH ₂ OH	CH ₃	H	CH ₂ OH	CH ₂ OH	CH ₃	OAc	OH	OH		(Bahrami and Franco, 2015)
<i>H. lessoni</i>	Lessonioside C	CH ₂ -OH	H	CH ₂ OH	CH ₃	H	H	CH ₃	=O	OH	OH		(Bahrami and Franco, 2015)
<i>H. lessoni</i>	Lessonioside D	CH ₃	CH ₂ OH	H	CH ₃	CH ₂ OH	CH ₂ OH	CH ₃	OAc	OH	OH		(Bahrami and Franco, 2015)
<i>H. lessoni</i>	Lessonioside E	CH ₃	CH ₂ OH	CH ₂ OH	H	H	H	CH ₃	=O	OH	OH		(Bahrami and Franco, 2015)
<i>H. lessoni</i>	Lessonioside F	CH ₃	CH ₂ OH	CH ₂ OH	H	CH ₂ OH	CH ₂ OH	CH ₃	=O	OH	OH		(Bahrami and Franco, 2015)
<i>H. lessoni</i>	Lessonioside G	CH ₂ -OH	H	CH ₂ OH	CH ₃	CH ₂ OH	CH ₂ OH	CH ₃	=O	OH	OH		(Bahrami and Franco, 2015)
<i>H. forskali</i>	Holothurinoside s F ₁	CH ₂ -OH	CH ₂ OH	CH ₂ OH	CH ₃	CH ₂ OH	CH ₃	H	H	H	H		(Honey-Escandón et al., 2015)
<i>H. forskali</i>	Holothurinoside s G ₁	CH ₂ -OH	CH ₂ OH	CH ₂ OH	CH ₃	CH ₂ OH	CH ₃	H	H	OH	H		(Honey-Escandón et al., 2015)
<i>H. forskali</i>	Holothurinoside s G	CH ₃	CH ₂ OH	CH ₂ OH	CH ₃	CH ₂ OH	CH ₃	H	H	OH	OH		(Honey-Escandón et al., 2015)

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

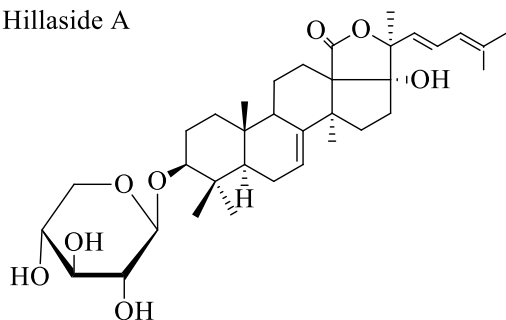
- Until now there is no triterpene glycosides with 3 β -hydroxyholost-8(9)-ene isolated from *Holothuria* genus.

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

2.2.3.1- Holostane glycosides contain 3 β -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 3 β -hydroxyholost-7(8)-ene with 4 sugar units isolated from *Holothuria* genus.

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

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

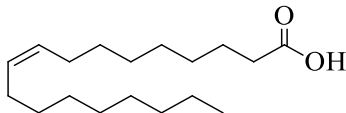
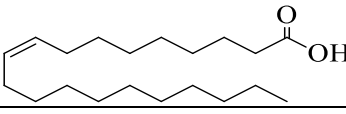
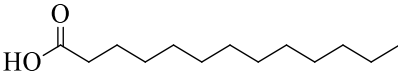
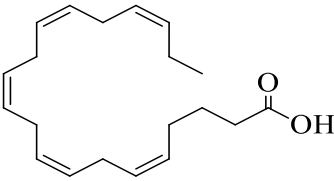
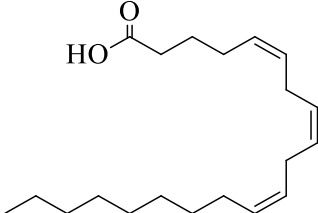
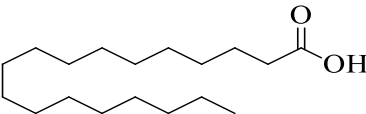
- Holostane glycosides contain 3 β -hydroxyholost-7(8)-ene with 6 sugar units oligosaccharide chain:

Up till now there is no triterpene glycosides with 3 β -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)

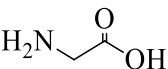
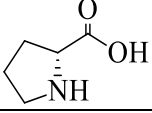
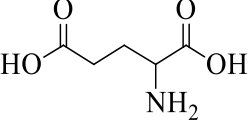
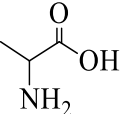
Table 7: Fatty acids reported in genus *Holothuria*

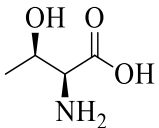
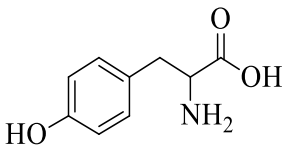
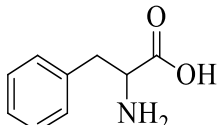
Species	Compound Name	Compound Structure	Reference
<i>H. Leucospilota</i> <i>H. sacbra</i>	Palmitic acid		(Ceesay <i>et al.</i> , 2019) (Yahyavi <i>et al.</i> , 2012)
<i>H. Leucospilota</i> <i>H. Sacbra</i> <i>H. tubulosa</i> , <i>H. mammata</i> <i>H. polii</i>	Arachidonic acid		(Yahyavi <i>et al.</i>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

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

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

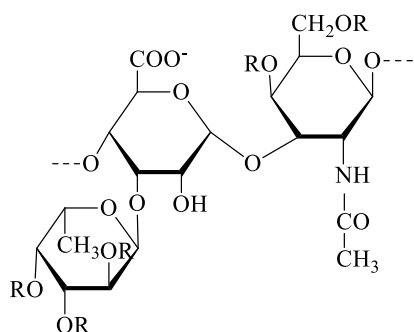
Table 8: Amino acids reported in genus *Holothuria*.

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

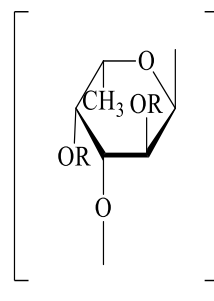
<i>H. fuscopunctata</i> , <i>H. fuscogilva</i>	Threonine		(Wen <i>et al.</i> , 2010)
<i>H. fuscopunctata</i> , <i>H. fuscogilva</i>	Tyrosine		(Wen <i>et al.</i> , 2010)
<i>H. fuscopunctata</i> , <i>H. fuscogilva</i>	Phenylalanine		(Wen <i>et al.</i> , 2010)

2.5 : Polysaccharides

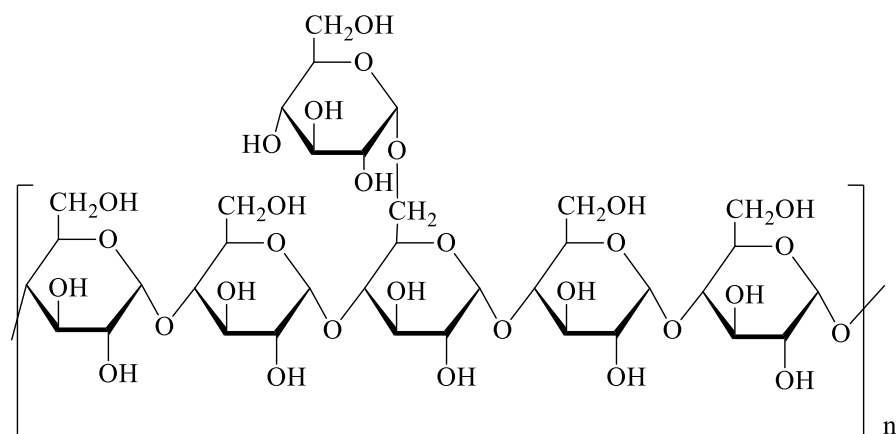
- There are two types of sea cucumber polysaccharides have been isolated fucosylated chondroitin sulfate (FuCS) and fucan sulfates which usually called fucoidans. The fucoidans structure is usually made from linear or branched ($\alpha 1 \rightarrow 3$)- and/or ($\alpha 1 \rightarrow 4$)-linked fucosyl 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).



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, SO₃, or a fucose or
galactose side chain.

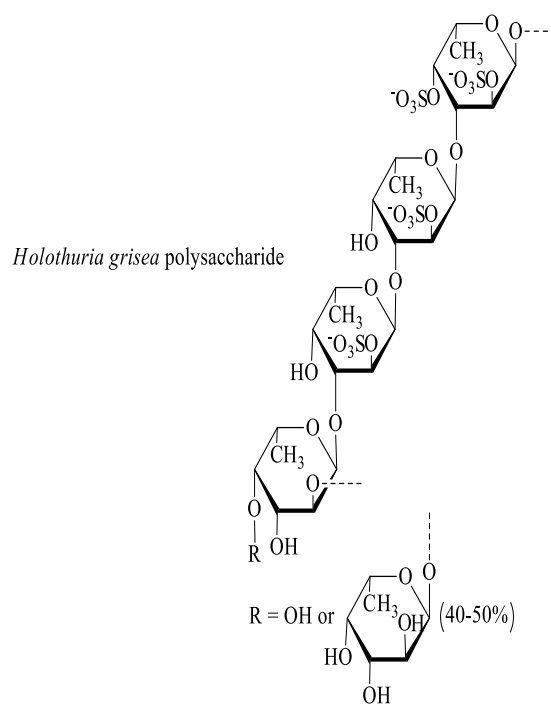
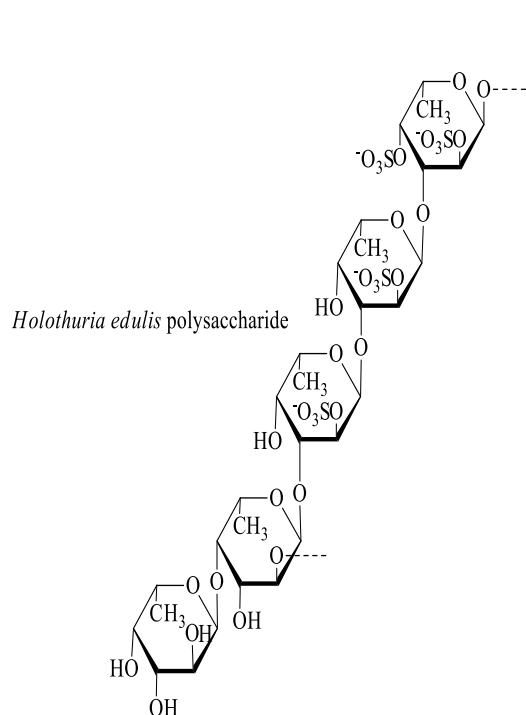


Holothuria edulis neutral glucan

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

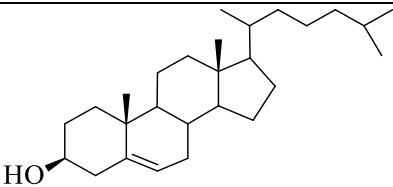
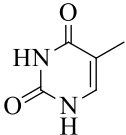
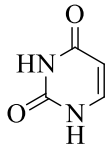
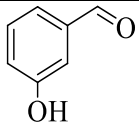
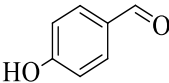
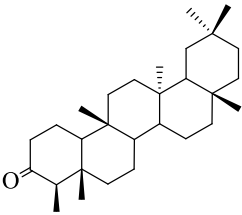
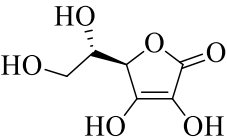
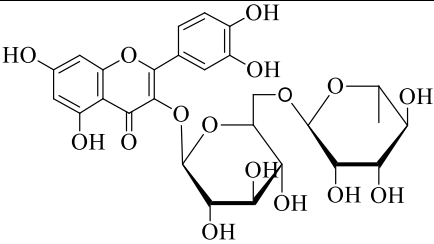
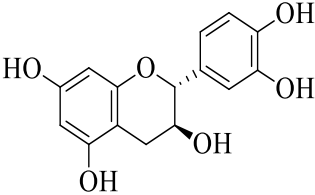
- Two sulfated fucans were isolated from *Ludwigothurea grisea* (*Holothuria grisea*) and *Holothuria edulis* sea cucumbers and their structures were illustrated by the combination of NMR spectroscopy, chemical analysis, methylation experiments and specific optical rotation. The two sulfated α -L-fucans are linear polysaccharides which consist of a

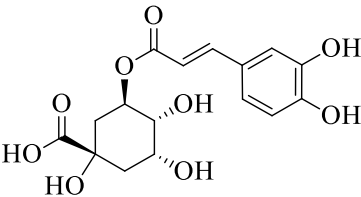
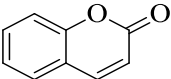
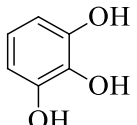
repeated tetrasaccharide backbone unit characterized by O-sulfation pattern with an unsulfated side chain fucose unit. All *H. edulis* α -L-fucan polysaccharides are fucosylated at position O-4 of the tetrasaccharide repeated unit but the *L.grisea* sulfated fucans are not all fucosylated at 4-position, only 40-50% are fucosylated at the backbone (Wu *et al.*, 2015).



2.6: Miscellaneous compounds:

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

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

<i>H. atra</i>	Chlorogenic acid		(Esmat <i>et al.</i> , 2013)
<i>H. atra</i>	Coumaric acid		(Esmat <i>et al.</i> , 2013)
<i>H. atra</i>	Pyrogallol		(Esmat <i>et al.</i> , 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.

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