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Review Article

Marine Sourced Bioactive Steroidal Compounds as Potential Cytotoxic Agents against Various Cancer Cell Lines

Sisir Nandi* and Ankita Sharma

Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research, Uttarakhand, India

ABSTRACT

To exploit the potential of the natural flora and fauna, it is urgent to study and unravel full chemical mysteries hidden in our vast natural diversity. Natural resources consist of large forest areas in diverse climatic zones, and also of the sea coast. Ocean covers 71% of the earth surface. Inspite of that, number of species on land is much higher than the oceans. About 16% of world's species lives in oceans, 80% on land and remaining lives in fresh water. There is a great need to expand the capabilities in these sea areas to remain globally relevant. More in-depth study, especially on deep-sea natural products, needs to be carried out to solidify the research on the potential for marine organisms to contribute to the future of drug discovery. Many potential drugs and lead compounds are discovered from the marine organisms. The present study is an attempt to summarize current marine sourced bioactive steroidal compounds as potential cytotoxic agents.

Keywords: Anticancer agents; Cytotoxicity; Sea-sourced steroidal compounds

INTRODUCTION

Ocean and sea are the rich sources of bioactive natural compounds. Marine is one of the very important sources of drug discovery research. But vast sea life is hidden and it is really difficult to identify the area of questioning the potential marine organisms. Marine organisms constitute nearly half of the worldwide biodiversity [1]. Living conditions in the lithosphere and hydrosphere are different. Meteorological parameters like temperature (from-1.5°C in ice sea to 350°C in deep hydrothermal systems), pressure (1 to over 1,000 atmospheres), light (complete darkness to extensive photic zones) and nutritional conditions (nutrient-rich till nutrient-sparse) and an huge number of different species are found in the sea and ocean [2] therefore marine bioactive compounds exhibit potential biological activity with unique structural features and can be considered safer to some existing synthetic drugs [3]. In contrast, only one of 5000-10,000 of the new synthetic molecules in development becomes a commercial pharmaceutical drug due to toxicity discovered in the clinical phases [4] so that reason marine natural compounds could be taken for developing pharmaceutical drugs having least toxicity and side effects. Marine organisms produce secondary metabolites because of biological and chemical diversity in the sea and oceans [5]. Marine natural products are generally primary and secondary metabolites. These metabolites possess antibacterial, immunomodulator, antifungal, anti-inflammatory, antioxidant, anticancer, antimicrobial, neuroprotective, analgesic, and anti-malarial properties [6] and they can control carcinogenesis by activating macrophages, inducing apoptosis, and prevent oxidative damage of DNA. Marine-sourced natural compounds have the potential to prevent or inhibit the growth of cancer cells hence they can be used for the new drug development. In this review, we focused on the steroidal marine natural compounds having cytotoxic activity. Natural compounds contain terpenoid derivatives, alkaloids, glycosides, polyphenolics, Steroids, polyketides, and peptides [7]. Generally, a large number of bioactive compounds are extracted from the marine invertebrates. Their extracts are further been examined for different cancer cell lines in the therapeutic areas of leukemia, breast, ovarian, renal, prostate, brain, colon, melanoma and lung cancers [8].

Steroids are lipophilic, low molecular weight compound derived from cholesterol. Steroids have cyclopenta[a]phenanthrene skeleton with methyl groups at C10 & C13 and an alkyl side chain is also present at C17. The stereochemistry of steroids shows a chair conformation. Steroids posses' vast range of structural and biological diversity, therefore, researchers are still searching secondary metabolites from steroids for the designing and discovery of lead molecules [9].

Correspondence to: Sisir Nandi, Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research, Kashipur-244713, Uttarakhand, India, Tel: +91 7500458478; E-mail: sisir.iicb@gmail.com

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MARINE-SOURCED STEROIDAL COMPOUNDS HAVING CYTOTOXIC ACTIVITY

The earth surface is covered by the 70% of the marine environment with huge biodiversity (consisting up to 36 phyla) and chemical diversity. Novel chemicals finding from marine resources are increasing every year. A Diverse array of marine organisms is used for producing pharmaceutical compounds. Researchers have isolated various bioactive compounds from various marine sources which are from marine animals such as fish, microorganisms, algae, sponges, coelenterates (sea whips, sea fans and soft corals), invertebrate phyla such as ascidian, molluscs (nudibranchs, sea hares, cone snail), echinoderms (starfish, sea cucumbers etc), bryozoans (moss animals), [9] and from symbiotic microorganism, for example, steroidal bioactive compound, 7β-hydroxycholesterol-1β-carboxylic acid with its two steroidal metabolites were yielded from a co-culture of marine alga-derived micro-organisms. 7β-hydroxycholesterol-1β-carboxylic acid possess cytotoxic activity against four different human tumor cell lines K562 (leukaemia), HCT116 (colon), A2780 (ovary) [10].

Steroidal cytotoxic compounds from marine mollusks

Lee Y. J et al. grinded and lyophilized whole-body tissue of cone snail *Conus pulicarius* and isolated three sulfate steroidal glycoside derivatives: Conusaponin A-C. These three derivatives showed *in-vitro* cytotoxicity against the human leukemia cell line K562 [11]. Figure 1 contains the structures of steroidal cytotoxic compounds from marine mollusks.

Steroidal cytotoxic compounds from marine sponges

Marine sponges are master producers. Marine sponges produce a wide variety of bioactive compounds. Symbiotic microorganism (bacteria and fungi) with marine sponges produce a wide range of bioactive compounds against foreign attackers. Symbiotic microorganisms synthesize secondary metabolite that acts as an antifouling, antiviral, antimalarial, anticancer agent [12]. The marine Sponges (belonging to Phylum Porifera) are an abundant source of bioactive compounds. Some of these compounds have cytotoxic activity towards certain types of malignant cells [13]**.** Halistanol trisulfate, a sulfated steroid was isolated from the extract of two sponges of genus *Topsentia*. Halistanol demelanize pigmented human melanoma cell line, MM418 [8].Two steroidal sulfates, eurysterols A and B, were isolated from the sponge genus *Euryspongia*. They possess cytotoxicity against human colon carcinoma (HCT-116) cells [IC_{50}=2.9] [14].Two polyhydroxylated sterol derivatives, topsensterols B and C have isolated from a marine sponge *Topsentia* sp. Topsensterol B exhibit significant cytotoxicity against human gastric carcinoma cell line SGC-7901 [IC_{50}=8.0 μM] while Topsensterol C exhibit cytotoxicity against human erythroleukemia cell line K562 [IC_{50}=6.0 μM] [15]. Marine sponge, *Cinachyrella anomala* posses a steroidal oxime (24R, 6E)-24-ethylcholest-6-hydroxyimino-4-EN-3-one. It induces cell-cycle arrest at the sub-G and G/M phases and causes inhibition of T47D cancerous cell [16,17]. The methanolic extract of the marine sponge *Ircinia echinata* posses six 9α-hydroxy-5α, 6α-epoxysterols derivatives but only two sterols: (24R)-5α, 6α-epoxy-24-ethyl-cholesta-7-en-3β,9α-diol and 5α,6α-epoxycholesta-7-en-3β,9α-diol showed cytotoxic activity. (24R)-5α, 6α-epoxy-24-ethyl-cholesta-7-en-3β, 9α-diol has shown significant anti-proliferative activity against three human cancer cell lines: MCF-7, Hep-G2 and LU-1 while 5α, 6α-epoxy-24-ethyl-cholesta-7-en-3β, 9α-diol is a selective inhibitor of human breast cancer cell MCF-7 [18]**.** Marine strain of *Gymnasella dankaliensis* isolated from sponge *Halichondria japonica* exhibit five steroids that showed significant inhibition against the lymphocytic leukemia P388 cell line [19]. Symbiotic fungi extract isolated from marine sponge *Neopetrosia chaliniformis AR-01* posses potent cytotoxic activity [20]. Figure 2 contains the structures of Steroidal cytotoxic compounds from marine sponges.

Steroidal cytotoxic compounds from marine coral

Eleven bioactive steroids were isolated from the soft coral *Umbellulifera petasites*. But only Petasitosterones A, petasitosterone C and 5α-pregna-1, 20-dien-3-one, are cytotoxic against the cancer cell lines human erythroleukemia (K-562), lymphoid T carcinoma (MOLT-4), human colorectal adenocarcinoma [21]. Another steroidal compound 7β-acetoxy-24-methylcholesta-5-24 (28)-diene-3,19-diol was isolated from soft coral *Nephthea chabroli* and 24-methylcholesta-5,24(28)-diene-3β,7β,19-triol was isolated from soft coral *Litophyton viridis* showed cytotoxic activity against prostate cancer cell line LNCaP, HT-29, KB, P-388 [22]. The bioactive compound from the extract of soft coral *Klyxum flaccidum* revealed four steroids klyflaccisteroids G-J having cytotoxic acidity against HT-29, P388 and K562 cancer cell lines [23]. Stoloniferones A-D is the cytotoxic steroids obtained from coral *Clavularia viridis*. The bioactive product of Soft corals *Alcyonum patagonicum* and *Nephtea erecta* is chemically polyoxygenated steroids which are cytotoxic to the human tumor cell lines CCRF-CEM and DLD1 [8]. Figure 3 contains the structures of Steroidal cytotoxic

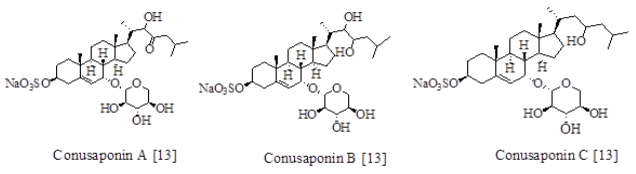

Figure 1: Structures of marine Mollusks.

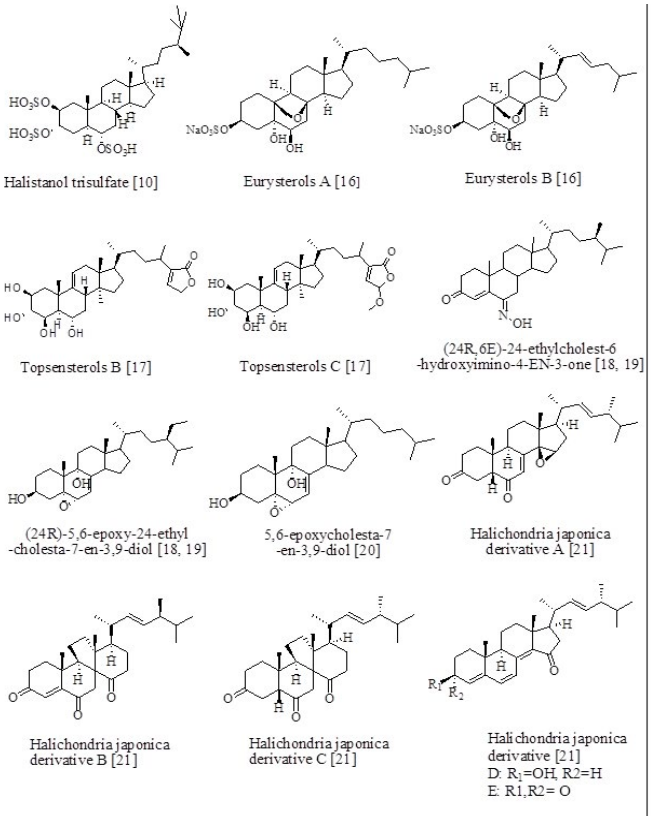

Figure 2: Structure of marine sponges.

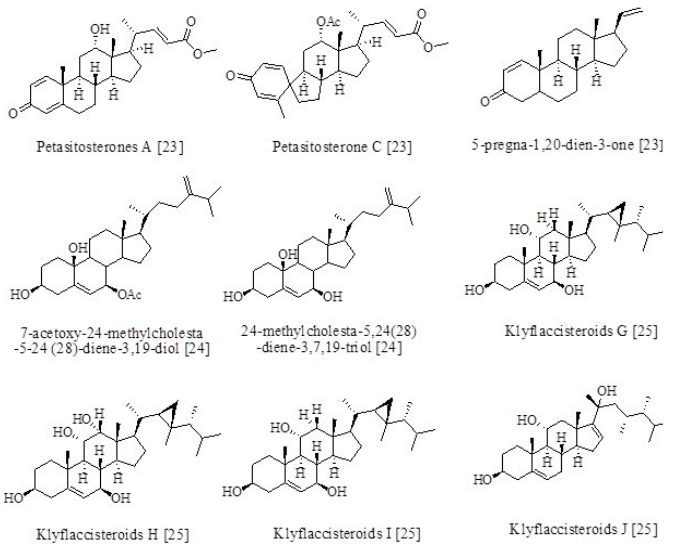

Figure 3: Structure of marine coral.

compounds from marine coral.

Steroidal cytotoxic compounds from marine Fungus

Various marine *Penicillium* species possess cytotoxic activity against cancer cell lines. Penicisteroide A was isolated from a marine alga-derived fungus, *Penicillum chrysogenum QEN-24S*. Penicisteroide A is a polyoxygenated steroid. It shows cytotoxic activity against Hela, SW1990, and NCI-H460 cell lines. Marine moss-derived fungus *Penicillium* species has three polyoxygenated steroids (*Penicillium* derivative 1-3) and two epidioxygenated steroids (*Penicillium* derivative 4-5). They inhibit HepG2 cell line growth. A sea squirt-derived fungus *P. stoloniferum QY2-10*, produce an epidioxygenated steroid (*Penicillium* derivative 6) which was cytotoxic to P388 cells. Four epimeric steroids, *Penicillium* derivative 7-8, and dankasterone A and B were isolated from unidentified sponge derived penicillum fungus. *Penicillium* derivative 7-8 and dankasterone B significantly inhibit K562 cell growth while dankasterone A was cytotoxic against HL-60, Hela, and K562 cancer cell lines [24]. The cytotoxic extract of marine fungus *Aspergillus ochraceus* found in macroalga *Sargassum kjellmanianum* posses 7-nor-ergosterolide (a nor-ergosteroid) and 3β,11α-dihydroxy ergosta- 8,24(28)-dien-7-one (steroid derivative). 7-nor-ergosterolide produce cytotoxic activity against NCI-H460, SMMC- 7721, and SW1990 human cancer cell lines whereas 3β, 11α-dihydroxy ergosta- 8,24(28)-dien-7-one weakly inhibit the growth of SMMC-7721 cells [25]. Figure 4 contains the structures of Steroidal cytotoxic compounds from marine fungus.

Steroidal cytotoxic compounds form marine echinoderm

Anthenosides derivatives (Anthenoside V,W,X,E,G,J,K,S1,S4,S6) containing steroidal glycoside moiety were isolated from the extract of the tropical starfish *Anthenea aspera*. *In-vitro,* there secondary metabolite can induce mitochondrial apoptosis in glioblastoma U87MG cells, inhibit human lung cancer A549 cells, induce p53-dependent apoptosis activities in human leukemia HL-60 and THP-1 cells, apoptosis in breast adenocarcinoma T-47D and colorectal carcinoma HT-29 cells [26,27]. Starfish *Culcita novaeguineae* contains three groups of steroidal metabolite: asterosaponins, polyhydroxysteroidal glycosides, and cyclic steroidal glycosides. Culcinosides A-D are polyhydroxy steroids and produces cytotoxicity against human glioblastoma cell lines U87, U251, and SHG44 [28]**.** (25S)-5α-cholestane-3β,5,6β,15α,16β,26-

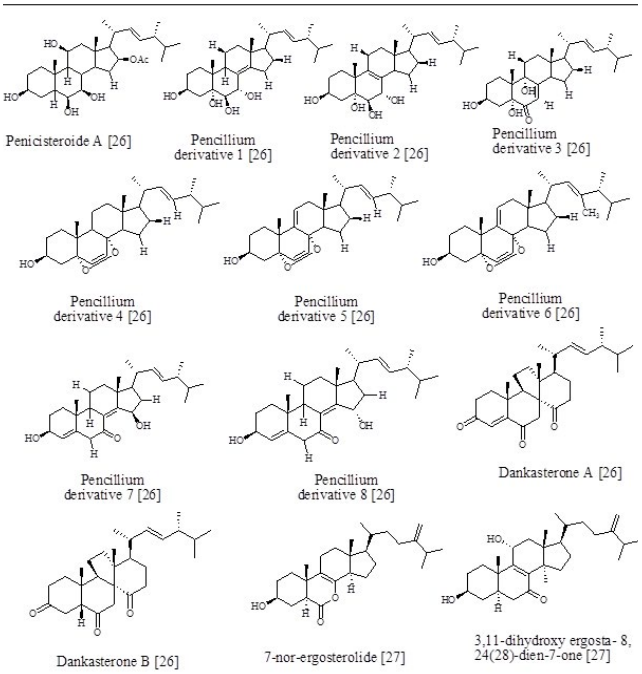

Figure 4: Structure of marine fungus.

hexaol isolated from cold water star fish *Ctenodiscus crispatus* showed cytotoxic activity against human hepatoma HepG2 and glioblastoma U87MG cells *via* inhibition of cell growth and induction of apoptosis [29,30]. Asteropectinol derivatives (Asteropectinol A, C, D, 5α-cholest-7-ene-3β,6α-diol and 5α-chole st-7,9(11)-d ie ne-3β-ol) were isolated from the methanolic extract of starfish *Astropecten polycanthus*. Asteropectinol derivatives exhibit moderate cytotoxicity against HL-60 (leukemia cancer cells), PC-3 (prostate cancer cells), SNU-C5 (colorectal cancer cells [30,31]. Four novel sulfated polyhydroxysteroids, leptaochotensosides A-C were isolated from the starfish *Leptasterias ochotensis.* leptaochotensoside A showed antiproliferative effect through the inhibition of phosphorylation of MAP kinases. Leptaochotensosides B-D slightly exhibits a cytotoxic effect on colony formation of T-47D cells [32]. A steroid biglycosides, Planciside A was extracted from the starfish Acanthaster planci. Planciside A inhibits proliferation of HCT-116, T-47D, and RPMI-7951 cancer cell lines [33]. Polyhydroxysteroids extracted from the starfish *Asterina pectinifera* were cytotoxic to the HL-60 cells and human liver carcinoma HepG2 cell line [34]. Figures 5 and 6 contain the structures of Steroidal cytotoxic compounds from marine echinoderm.

Special care should be taken utilizing modern sophisticated tools such as GC-MS, LC-MS, HPLC-MS and HPTLC-MS when performing isolation procedures adapted to the physical and chemical characteristics of these marine sourced compounds isolated, particularly their lipo- or hydrophilic characters. Purification and structure elucidation can be achieved using recent spectroscopic techniques, especially 2D NMR and mass spectrometry analysis.

CONCLUSION

The discovery during the mid-last century of the first marine steroids with unprecedented structures has opened a large avenue of marine investigations. Drug resistance remains as one of the most important disadvantages of cancer chemotherapy. In order to conquer drug resistance or multidrug resistance, the above drawbacks should be minimized by developing more effective

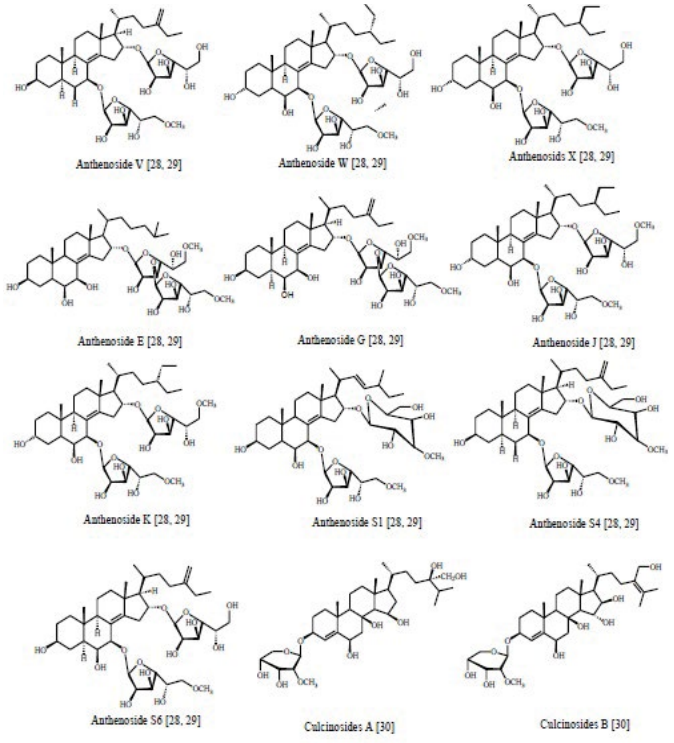

Figure 5: Structures of marine echinoderm.

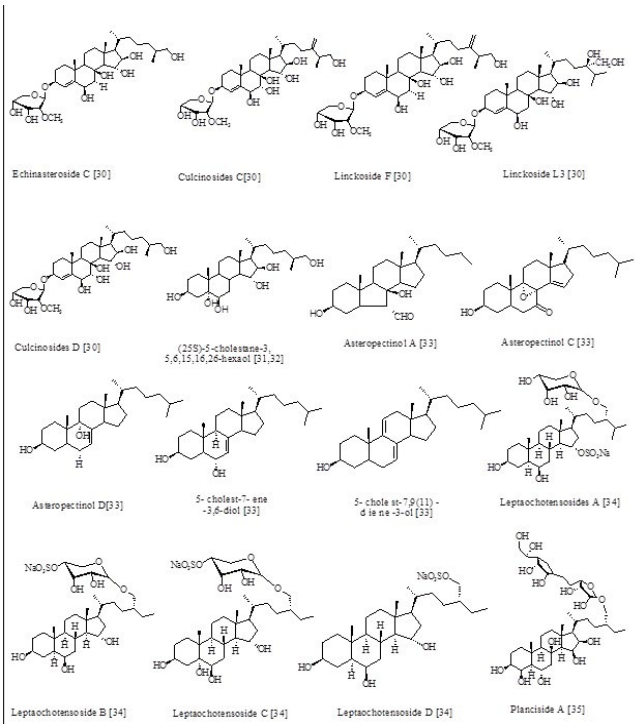

Figure 6: Structures of marine echinoderm.

site specific drug delivery systems which can significantly improve the therapeutic efficacy to chemotherapeutic drugs with minimal toxicity. The present study is an attempt to discuss marine sourced bioactive steroidal compounds having potential cytotoxicity against various cancer cell lines such as prostate cancer, ovarian cancer, lung cancer, colon cancer, and leukemia. These compounds may be taken as a template for the future perspective of combinatorial library design and screening of potential anticancer congeneric leads utilizing chemometric tools. Providing an outlook into the future, an attempt could also be made to examine the advances in existed compounds having promising cytotoxicity and these may further expand the promise of drugs against another disease by the application of in-silico screening through drug repositioning. The newly designed could be synthesized and *in-vitro* biological activity testing followed by *in-vivo* animal screening. Additionally, successful results on cell lines (*in-vitro*) may not always result in successful anti-cancer activity *in-vivo*. In this connection, it is important to note that squalamine is being currently under advanced clinical trials for the treatment of ovarian cancer and also of age-related macular degeneration.

REFERENCES

1. Hamed I, Ozogul F, Ozogu Y, Regenstein JM. Marine bioactive compounds and their health benefits: A review. Compr Rev Food Sci Food Saf. 2015;14:446-461.
2. Lindequist U. Marine-derived pharmaceuticals-challenges and opportunities. Biomol Ther. 2016;24:561-571.
3. Suleria HAR, Gobea G, Mascia P, Osborne SA. Marine bioactive compounds and health promoting perspectives; innovation pathways for drug discovery. Trends Food Sci Technol. 2016;50:44-55.
4. Ruiz-Torres V, Encinar JA, Herranz-López M, Almudena Pérez-Sánchez A, Galiano V, Barrajón-Catalán E, et al. An updated review on marine anticancer compounds: The use of virtual screening for the discovery of small-molecule cancer drugs. Molecules. 2017;22:1037-1074.
5. Kijjoa A, Sawangwong P. Drugs and cosmetics from the sea. Mar Drugs. 2004;2:73-82.
6. Malve H. Exploring the ocean for new drug developments: Marine pharmacology. J Pharm Bioall Sci. 2016;8:83-91.
7. Boopathy NS, Kathiresan K. Anticancer drugs from marine flora: An overview. J Oncology. 2010;1:1-18.
8. Datta D, Talapatra SN, Swarnakar. Bioactive compounds from marine invertebrates for potential medicines-An overview. Int lett nat sci. 2015;7:42-61.
9. Sultan A, Raza AR. Steroids: A diverse class of secondary metabolites. Med chem. 2015;5:310-317.
10. Ebada SS, Fischer T, Klaben S, Hamacher A, Roth YO, Kassack MU, et al. A new cytotoxic steroid from co-fermentation of two marine alga-derived micro-organisms. Nat Prod Res. 2014;28:1241-5.
11. Lee YJ, Han S, Kim SH, Lee HS, Shin HJ, Lee JS, et al. Three new cytotoxic steroidal glycosides isolated from conus pulicarius collected in Kosrae, Micronesia. Mar Drugs. 2017;15:379-387.
12. Kamalakkannan P. Marine sponges a good source of bioactive compounds in anticancer agents. Int J Pharm Sci Rev Res. 2015;31:132-135.
13. Mioso R, Marante FJ, Bezerra RS, Borges FV, Santos BV, Laguna IH. Cytotoxic compounds derived from marine sponges. A review (2010-2012). Molecules. 2017;22:208-242.
14. Boonlarppradab C, Faulkner DJ. Eurysterols A and B, cytotoxic and antifungal steroidal sulfates from a marine sponge of the genus *Euryspongia*. J Nat Prod. 2007;70:846-848.
15. Chen M, Wu XD, Zhao Q, Wang CY. Topsensterols A-C, cytotoxic polyhydroxylated sterol derivatives from a marine sponge *Topsentia* sp. Mar Drugs. 2016;14:146-154.
16. Kovganko NB, Chernov YG. Novel synthesis of (24R, 6E)-24-ethylcholest-6-hydroxyimino-4-EN-3-one, a steroidal oxime from *Cinachyrella* spp. Sponges. Chem Nat Compd. 2000;36:189-191.
17. Nurhayati APD, Pratiwi R, Wahyuono S, Purnomo IH, Abdillahz S. *In-Vitro* test and molecular docking of alkaloid compound in marine sponge *Cinachyrella anomala* against T47D cell cycle. J Marine Sci Res

Dev. 2015;5:1-3.

18. Trinh TTV, Truong BN, Longeon A, Doan TMH, Deville A, Chau VM, et al. New 9-Hydroxy-5,6-epoxyhydroxyl sterols from, the Vietnamese marine sponge *Ircinia echinata*. Mar Drugs. 2018;16:424-434.

19. Zhang H, Zhao Z, Wang H. Cytotoxic natural products from marine sponge-derived microorganisms. Mar Drugs. 2017;15:68-81.

20. Handayani D, Artasasta MA. Antibacterial and cytotoxic activities screening of symbiotic fungi extract isolated from marine sponge *Neopetrosia chaliniformis* AR-01. J Appl Pharm Sci. 2017;7:66-69.

21. Huang CY, Chang CW, Tseng YJ, Lee J, Sung PJ, Su JH, et al. Bioactive steroids from the formosan soft coral *Umbellulifera petasites*. Mar Drugs. 2016;14:180-91.

22. Ellithey MS, Ahmed HH. Bioactive marine-derived compounds as potential anticancer candidates. Asian J Pharm Clin Res. 2018;11:464-466.

23. Tseng WR, Huang CY, Tsai YY, Lin YS, Hwang TL, Su JH, et al. New cytotoxic and anti-inflammatory steroids from the soft coral *Klyxum flaccidum*. Bioorg Med Chem Lett. 2015;26:3253-3257.

24. Liu S, Su M, Song SJ, Jung JH. Marine-derived *Penicillium* species as producers of cytotoxic metabolites. Mar Drugs. 2017;15:329.

25. Sarasan M, Puthumana J, Job N, Han J, Lee JS, Philip R. Marine algicolous endophytic fungi-A promising drug resource of the era. J Microbiol Biotechnol. 2017;27:1039-1052.

26. Malyarenko T, Malyarenko O, Kicha A, Ivanchina N, Kalinovsky A, Dmitrenok P, et al. *In-vitro* anticancer and proapoptotic activities of steroidal glycosides from the starfish *Anthenea aspera*. Mar Drugs. 2018;16:420-434.

27. Malyarenko T, Ivanchina N, Malyarenko O, Kalinovsky A, Dmitrenok P, Evtushenko E, et al. Two new steroidal monoglycosides, anthenosides A1 and A2, and revision of the structure of known anthenoside A with unusual monosaccharide residue from the starfish *Anthenea aspera*. Molecules. 2018;23:1077-1089.

28. Lu Y, Li H, Wang M, Liu Y, Feng Y, Liu K, et al. Cytotoxic polyhydroxysteroidal glycosides from starfish *Culcita novaeguineae*. Mar Drugs. 2018;6:92-102.

29. Quang TH, Lee DS, Han SJ, Kim C, Yim JH, Kim YC, et al. Steroids from the cold water starfish *Ctenodiscus crispatus* with cytotoxic and apoptotic effects on human hepatocellular carcinoma and glioblastoma cells. Chem Inform. 2014;35:2335-2341.

30. Sumithaa R, Banu N, Deepa V. Novel natural products from marine sea stars. Curr Trends Biomedical Eng Biosci. 2017;2:1-5.

31. Thao NP, Cuong NX, Luyen BTT, Nam NH, Cuong PV. Steroidal constituents from the starfish *Astropecten polyacanthus* and their anticancer effects. Chem Pharm Bull. 2013;61:1044-1051.

32. Malyarenko MV, Malyarenko OS, Ivanchina NV, Kalinovsky AI, Popov RS, Kicha A. Four new sulfated polar steroids from the far eastern starfish *Leptasterias ochotensis*: Structures and activities. Mar Drugs. 2015;13:4418-4435.

33. Kichaa AA, Dinhb TH, Ivanchinaa NV, Malyarenkoa TV, Kalinovskya AI, Popov RS, et al. Three new steroid biglycosides, plancisides A, B, and C, from the starfish *Acanthaster planci*. Nat Prod Commun. 2014;9:1269-1274.

34. Wikarta JM, Kim SM. Anti-inflammatory activity and cytotoxicity of the starfish extracts on cancer cells in culture. Med chem. 2016;6:331-338.