Review
Secondary Metabolites from the Marine Sponges of the Genus Petrosia: A Literature Review of 43 Years of Research

Yeon-Ju Lee 1,2,*, Yeonwoo Cho 1,2 and Huynh Nguyen Khanh Tran 1

1 Marine Natural Products Chemistry Laboratory, Korea Institute of Ocean Science and Technology, 385 Haeyangro, Busan 49111, Korea; yeonwoo@kiost.ac.kr (Y.C.); hnktran@kiost.ac.kr (H.N.K.T.)
2 Department of Applied Ocean Science, University of Science and Technology, Daejeon 34113, Korea
* Correspondence: yjlee@kiost.ac.kr; Tel.: +82-51-664-3350

Abstract: Sponges are prolific sources of various natural products that have provided the chemical scaffolds for new drugs. The sponges of the genus Petrosia inhabit various regions and contain a variety of biologically active natural products such as polyacetylenes, sterols, meroterpenoids, and alkaloids. This review aims to provide a comprehensive summary of the chemical structures and biological activities of Petrosia metabolites covering a period of more than four decades (between 1978 and 2020). It is also described in this review that the major groups of metabolites from members of the genus Petrosia differed with latitude. The polyacetylenes were identified to be the most predominant metabolites in Petrosia sponges in temperate regions, while tropical Petrosia species were sources of a greater variety of metabolites, such as meroterpenoids, sterols, polyacetylenes, and alkaloids.

Keywords: Petrosia; metabolite; geography; polyacetylene; sponge

1. Introduction

The oceans represent the largest habitat on earth and contain organisms with high biological and chemical diversity. The secondary metabolites of diverse marine organisms allowed these species to develop mechanisms that would enable them to survive in the ocean. Over 30,000 natural products have been isolated from marine organisms [1], and 1490 and 1554 new compounds were discovered recently as 2017 and 2018, respectively [2,3].

Marine invertebrates, such as sponges, cnidarians, bryozoans, echinoderms, and tunicates, exclusively inhabit aquatic environments [4]. They are either sessile or slow moving, have soft bodies, and lack morphological defense structures such as shells or thorns [5]. Therefore, it is not incidental that these organisms evolved chemical defense mechanisms against predation and overgrowth of fouling organisms [6,7]. The abundance and diversity of secondary metabolites synthesized for chemical defense provide an opportunity to examine the chemical entities with potential therapeutic applications.

Marine sponges (Porifera) have been the central focus of the research for the discovery of biologically-active secondary metabolites. As sponges are highly effective filter feeders, microorganisms in the surrounding water are actively swirled by the sponge-driven currents. While some of the microorganisms are immediately digested, others are retained within the sponge body. It was reported that associated microorganisms can account for up to 60% of the fresh weight of marine sponges, and are more diverse than can be estimated using current technology [8,9]. It is believed that these sponge-associated microorganisms such as bacteria, fungi, cyanobacteria, and unicellular algae may be involved in the biosynthesis of natural products that are isolated from the sponges, although the relationship between sponge and associated microorganisms are highly complex [10].
Several statistical studies on marine natural products have revealed that sponges are outstanding in number of isolated biologically-active compounds. Hu et al. have analyzed the temporal trend, chemical structure distribution, bioactivity groups, and species distribution of biologically-active compounds from marine organisms discovered during the 28 years from 1985 to 2012 [11]. In this study, the authors found out that approximately 75% of the compounds were isolated from marine invertebrates, and the highest proportion of bioactive compounds had been isolated from sponges. Another report, which covers 9812 marine natural products isolated from invertebrates discovered during 1990–2009, also showed that the highest proportion of metabolites could be traced to sponges (48.8%) [12].

It is generally believed that there is a higher chance of discovering biologically-active sponge metabolites in habitats characterized by intense competition for survival due to their high biological diversity and density, such as coral reefs in tropical regions [13,14]. Following the principle that sponge chemical defense is mainly driven by predation pressure [15], it was hypothesized that chemical diversity is higher in the tropical region than the temperate region. This hypothesis is only partly supported, as it was reported that tropical and temperate benthic systems differ with regard to dominant consumption regimes. While fishes are dominant predators on reefs in tropical regions, temperate systems are characterized by mesopredators such as crustaceans, sea urchins, and gastropods [16,17].

Geographical location is clearly one of the most influential factors related to the variation in sponge metabolites; however, few studies have investigated the geographical variation in sponge metabolites in terms of yield or biological activity. The first study regarding this issue claimed the inverse relationship between latitude and toxicity in sponges [18]. The authors examined the toxicity of 78 sponge species collected in temperate (San Juan Island and Santa Catalina Island) and tropical regions (La Blanquilla reef and Zihuatanejo Bay) on fishes by measuring the time from exposure to death. They found that 9% of the sponge species in the regions of 48 degrees north were toxic and 75% of the sponges studied in the region of 19 degrees north were toxic. A study by Ruzicka et al. also demonstrated that sponge species on the temperate reefs in the South Atlantic Bight are a smaller chemical deterrent to fish predators than their counterparts at lower latitudes in the Florida Keys by measuring the palatability of sponge crude extracts quantitatively and comparing the results with those obtained by Pawlik et al. [14,19].

Results that are contradictory to those above have also been reported. A feeding assay with 17 pairwise comparisons conducted by Burns et al. showed no significant differences in deterrence between Red Sea and Caribbean sponges [20]. The field-based feeding experiments with diverse fish predators conducted by Becerro et al. showed similar results [21]. When 20 sponge species from tropical Guam and temperate Northeast Spanish coasts were compared, no significant difference was observed based on habitat. It is worthwhile to mention, however, that the percentage yield of crude organic extracts tends to be proportional to latitude, although the authors did not provide any comment on this. When a total of 20 sponge species in 10 species pairs were extracted, the tropical sponges were found to provide up to a 3.4 times higher yield than their temperate counterparts in nine pairs.

More recent studies focused on the intra-specific variability in secondary metabolites in terms of concentration. One such study examined Aplysina aerophoba, a common Mediterranean sponge known to contain large concentrations of brominated alkaloids [22]. When the concentrations of bromotyrosine alkaloids such as aerophobin-1, aerophobin-2, aplysinaminis-1, and isofistularin-3 were evaluated using HPLC according to the geographic location of its habitat, significant variation was observed at the largest (Canary Islands and Mediterranean, over 2500 km) and the smallest (two sites less than 500 m apart) geographic scales. Another study evaluating the variability in metabolites of Stylissa massa came to a similar conclusion [23]. The concentrations of the bromopyrrole alkaloids—e.g., hymenidine analogs, sceptrin, and oroidin—were measured using LC-MS
analysis. Concentrations varied geographically across the Pacific basin, with American Samoa and Pohnpei exhibiting the greatest differences, and Guam and Saipan being the most similar to each other.

A very recent metabolomics study revealed the relationship between sponge metabolites and the geographic location. Total 139 specimens of Xestospongia spp. were collected in four locations—Martinique, Curacao, Taiwan, and Tanzania—and the extracts were analyzed by 1H NMR and LC-MS, followed by statistical analysis (OPLS-DA); the collected samples were clearly grouped according to their location [24].

Experimental evidence supports this geographical trend of the sponge metabolites, although it is scattered throughout the literature. This review aims to compile this information and determine variations in metabolites according to geographical location using the genus Petrosia. Petrosia is one of the four genera (Acanthostrongylophora, Neopetrosia, Petrosia, Xestospongia) of the family Petrosiidae belonging to the order Haplosclerida, which is known as the most prolific source of secondary metabolites among sponges [12]. As of 2020, Petrosia genus includes 122 species belonging to two subgenera of Petrosia and Strongylophora, according to the Word Register of Marine Species (WoRMS). They are widely distributed throughout tropical and temperate waters, from intertidal zones to deep waters.

This review collects and compares information from peer-reviewed articles on secondary metabolites isolated from the sponges of the genus Petrosia. The articles were retrieved from the following databases: PubMed, Chemical Abstracts®, ISI Web of Knowledge, Google Scholar. Based on the assumption that the latitude of sponge habitat plays an important role in the metabolite, the regions were divided into polar (above the Arctic Circle (66.5° N) and below the Antarctic Circle (66.5° S)), temperate (between the Tropic of Cancer (23.5° N) and the Arctic Circle and between the Tropic of Capricorn (23.5° S) and the Antarctic Circle), and tropical area (between the Tropic of Cancer and the Tropic of Capricorn).

2. Petrosia Metabolites
2.1. Polyacetylenes

Polyacetylenes are characteristic metabolites of Petrosia sponges inhabiting temperate regions above the Tropic of Cancer. Of the 38 publications regarding the secondary metabolites from temperate Petrosia sponges, 31 reported the isolation of polyacetylenes.

Mixtures of high-molecular weight polyacetylenes with 46–55 carbons were isolated from both the sponge P. ficiformis and its predator nudibranch Peltodoris atromaculata [25] in the Mediterranean Sea. These were the first reported polyacetylenes from Petrosia sponges, although some of the structural features of these—e.g., the aliphatic carbon chain length between the characteristic functional groups and stereochemistry—were not revealed. Five years later, the same research group isolated small amounts of two additional polyacetylenes, but their structural assignment remained incomplete [26]. Mixtures of five additional polyacetylenes up to 52 carbons long, isolated from P. ficiformis found in dark caves in the Mediterranean Sea, were also reported [27].

In 1989, polyacetylenes with two terminal 1-yn-3-ol-4-ene moieties and 46 total carbons isolated from Mediterranean P. ficiformis were completely identified and evaluated for their biological activity (Figure 1); the structures of petroformynes 1–4 (1–4) were elucidated, and it was shown that they inhibit sea urchin egg development and act as a potent toxin against Artemia salina [28]. The absolute stereochemistry of petroformynes was later elucidated by Mosher's method [29]. The minor analogs contained in the same species were added through further research [30–32]; petroformynes, isopetroformynes, and various oxidized or isomerized analogs (5–22) were reported. Most of these analogs exhibited lethality against brine shrimp.
Polyacetylene carboxylic acids—petroformynes A, B (23, 24), and petroformynic acid (25)—were also reported [32]. Compounds 23 and 24 showed high lethality in brine shrimp assay. Compounds 23 and 24 showed high lethality in brine shrimp assay.

Figure 1. Polyacetylenes isolated from Mediterranean *Petrosia* sponges.

Isolation of polyacetylenes from *Petrosia* sp. inhabiting temperate regions of Japan was initiated from the discovery of the C30 polyacetylenes, petrosynol (26) and petrosynone (27) (Figure 2) [33,34]. In the case of petrosynol (26), the stereochemistry of hydroxymethine was revealed by measuring the Cotton effect of benzylic derivatives. This was the first report to completely elucidate the structure of polyacetylenes, including stereochemistry. Four more petrosynol derivatives (28–31) were reported by another research group [35]. These compounds inhibited the cell division of fertilized ascidian (*Styela partita*) eggs with IC₅₀ values of 5.0–30.0 µg/mL and displayed toxicity in the brine shrimp lethality bioassay with LC₅₀ values from 0.1–30.0 µg/mL. Petroacetylene (32), a tetraketone derivative of 29 and 30, was also reported by a different research group [36].

The petroformyne analogs were also isolated from a Japanese *Petrosia* sponge; petroformynes 1 and 4 (1, 4) [37], in addition to the novel derivatives, neopetroformynes (33–36), were isolated [38]. The functional groups were identified based on NMR spectroscopy data including those from 2D NMR experiments such as COSY, HMBC, and TOCSY. The length of the alkyl chains was determined by analyzing FAB-MS/MS data and stereochemistry, except for that of neopetroformyne D (36), was revealed by the modified Mosher
In this report, the authors suggested that neopetroformyne A (33) and petroformyne 1 (I) might share the same structures, as their NMR data were indistinguishable. The structure of I, however, could not be reexamined by FAB-MS/MS due to a lack of remaining material. Neopetroformynes A–D (33–36) exhibited cytotoxicity against P388 murine leukemia cells with an IC₅₀ values in ranging from 0.09 to 0.45 µg/mL.

Figure 2. Polycyetylenic alcohols isolated from Japanese Petrosia sponges.

The related analogs, named durynes (37–42), were reported by the same research group [39]. Compound 37 ((–)-duryne) was found to be an enantiomer of (+)-duryne, which has previously been isolated from the marine sponge Cribrochalina dura collected off the shore of Staniel Cay (24.2° N) in the Bahamas [40]. The taxonomy of Cribrochalina dura was later revised to be Petrosia, and the absolute configuration of each enantiomer was confirmed by the synthesis of both enantiomers [41].

Miyakosynes are also allyl propargyl alcohols or ketones like petroformyne derivatives, but they have a branched methyl group in the aliphatic chain in the middle. Six miyakosynes (A–F, 43–48) were isolated from the sponge Petrosia sp. collected at Miyako sea knoll in Japan [42]. The locations of methyl branches were determined by tandem FAB-MS/MS analysis, and the stereochemistry was assigned using the modified Mosher’s method. Compounds 43–46 and a mixture of 47 and 48 exhibited cytotoxicity against HeLa cells with IC₅₀ values of 0.10, 0.13, 0.04, 0.15, and 0.30 µg/mL.

Petrosynes (49, 50) are polycyetylenic enol ethers isolated from a Petrosia sp. collected near Ishigaki Island (Figure 3) [43]. Followed by the deduction of the plane structure by spectroscopic analysis, all possible stereoisomers of 49 and 50 were synthesized enanti oselectively, which showed both to consist of mixtures of 7R and 7S diastereomers.
Polyacetylene carboxylic acids are another group of compounds isolated from Japanese Petrosia sponges. Five corticatic acids (51–55), which show antifungal activity against Mortierella ramanniana or Candida albicans, have been isolated from P. corticata [44,45]. Petroformylic acids B and C (56, 57)—analogous to petroformynes 4 and 3 (4, 3), respectively—were isolated along with petroformynes 1 and 4 (1, 4) [37]. Compounds 56 and 57 inhibited the growth of P388 cells with an IC$_{50}$ value of 0.4 µg/mL.

Polyacetylenes isolated from Petrosia inhabiting Korean water are mostly petroformyne 1 (I) and petrosynol (26) analogs, which have at least one allyl propargyl alcohol at the terminus (Figure 4). Petrocortynes A–H (58–65) were isolated from the extract of Petrosia sp. collected along offshore from Keomun Island, South Sea of Korea [46,47]. The structures of these compounds were elucidated by extensive NMR experiments, including COSY, HETCOR, HMQC, HMBC, and TOCSY, and the stereochemistry was revealed by a modified Mosher’s method. Petrocortyne C (60) possesses an unusual γ-pyrene ring, while the other analogs are linear C46 tetraacetylenes with a diacetylenic carbonyl functionality in the middle. Petrocortynes A–C (58–60) showed significant brine-shrimp lethality and RNA-cleaving activity and petrocortynes D–H (61–65) exhibited moderate to minimal cytotoxicity against a human leukemia cell line (K562) with LC$_{50}$ values of 7.0–45.0 µM.

Derivatives of the above mentioned petrocortynes appear in the several reports regarding Korean Petrosia sponges. Isolation of (3S, 14S)-petrocrtyne A (66), nor-(3S,14S)-petrocrtyne A (67), and petrotetrayndiols A–C (68–70) from the Petrosia inhabiting the same area was later reported [48,49]. Additional petrocrtynes (71–77) and petrotetrayndiol derivatives (78–83) were isolated and reported by another research group [50,51]. Most of these compounds showed high cytotoxicity against several human solid tumor cell lines.

Seo et al. reported the isolation of C30 polyacetylenes analogous to petrosynol (26) from the above mentioned Petrosia sp. collected near Keomun Island (Figure 5) and named these petrosiacetylenes A–D (84–87) [46]. Compounds 86 and 87 are mixtures of diastereomers at C-28. In the same year, another research group reported the compounds of the
same type (dideoxypetrosynols A–D) along with petrosynol (26) and duryne (37) [52]. Dideoxypetrosynols A–C later turned out to be the same compounds as petrosiacetylenes A (84), C (86), and B (85), respectively, although the diasteromeric ratio of petrosiacetylene C (28S:28R = 60:40) and dideoxypetrosynol B (28S:28R = 50:50) were slightly different. Dideoxypetrosynol D (88) was also a mixture of 28S and 28R diastereomers. Additional dideoxypetrosynols (89, 90) were reported, although the positions of multiple bonds and the stereochemistry have not been revealed [48]. Petrosiacetylene E (91) was isolated and its structure was completely elucidated [53]. Compared to analogous petrosiacetylenes A (84) and C (86), compound 91 showed three times higher cytotoxicity against a panel of human cancer cell lines, which emphasized the importance of the hydroxygroup at C-15.

**Figure 4.** Petrocortyne derivatives isolated from Korean Petrosia sponges.
Figure 5. Petrosiacetylenes isolated from Korean Petrosia sponges.

Novel enol ether glycerides (92–97) were isolated from the above mentioned Petrosia sponge collected near Keomun Island, along with analogous raspailynes and isoraspailynes (98–101) which have previously been isolated from the sponges Raspailia pumila and Raspailia ramosa (Figure 6) [54,55]. In the measurement of cytotoxicity against a human leukemia cell line (K562), the yne-diene derivatives (92–94) exhibited weak activity (LC50 9.2, 57.0, and 29.0 µg/mL, respectively), while the derivatives 95–97, possessing the yne-ene moiety, were not active. The carboxylate (102), which has an acetylenic alcohol moiety and a linear C12 carbon chain, was also reported in the same paper. This is reminiscent of petroformynes (23, 24) and petroformylic acid (25), which were isolated from Mediterranean P. ficiformis.

Figure 6. Polyacetylenic enol ether glycerides and carboxylates isolated from Korean Petrosia sponges.

2.1.2. Polyacetylenes Isolated from Tropical Petrosia Sponges

Several polyacetylenes have been isolated from tropical Petrosia sponges, although not as many as those from their counterparts in temperate regions. These compounds can
be categorized into two groups: one comprised of compounds bearing a diynol group and the other comprised of enyne carboxylates.

Alcohols with 2,4-diyne (the first group) were isolated from the Okinawan sponges of Petrosia genus (Figure 7). Strongyloidiols A–J (103–112) were isolated from an Okinawan Strongylophora sponge that was later revised as Petrosia [56,57]. These compounds were isolated as mixtures of enantiomers at C-6, which were resolved by modified Mosher’s method.

Analogous triols, strongylotriols (113, 114), and pellynols (115–117) were also isolated from an Okinawan Petrosia sponge [58]. The strongylotriols were found to be optically pure, whereas the pellynols were diasteromeric mixtures at C-6. The strongylotriols and pellynols exhibited different levels of cytotoxicity against HeLa and K562 cell lines; strongylotriols A and B (113, 114) exhibited IC50 values of 11.3–18.1 μM, and pellynols A, B and J (115–117) exhibited IC50 values of 0.5–0.6 μM.

The tetraol derivatives, petrosiols (118–122), were isolated along with strongyloidiols C and D (105, 106) from an extract of the Okinawan sponge P. strongylata [59]. The stereochmistry of the petrosiols was determined by derivatizing petrosiol C (120); 120 was hydrogenated using a Pt catalyst to provide the fully saturated derivative, then the stereochmistry of the product was assigned by comparing its 1H NMR to those of the four stereoisomers of 1,2,6,7-decanetetraol provided in Kishi’s Universal NMR databases [60]. Petrosiols (118–122) induced nerve growth factor-like neuronal differentiation of PC12 cells, which suggested the importance of the rare 2,4-diyne-1,6,7,8-tetraol fragment in neurotrophic activity.

The same type of acetylenic alcohols (123–131) were additionally isolated from an Okinawan Petrosia sp. [61]. In the regarding report, it is described that the position of the central double bonds in compounds was revealed by chemical transformation—the oxidative cleavage of the olefin, followed by the transformation of resulting aldehyde into the corresponding 2,4-dinitrophenylhydrazone. The analysis of the HRMS and 13C-NMR spectral data of each resulting hydrazones clarified the position of the central double bonds in 123–131.

Additional 2,4-diyn-1-ols were also isolated from Petrosia sponges growing in other tropical areas. Durissimols A and B (132–133) were isolated from P. durissima collected in Taiwan, along with the previously reported derivatives (37, 134–136) isolated from Reniera fulva [62]. Among the compounds isolated, duryne (37) and durissimol B (133) exhibited potent cytotoxicity against human gastric cancer cells (NUGC). Pellynol derivatives (115, 137–140) were isolated from a Petrosia sp. collected in American Samoa [63].

Enyne carboxylates (141–144), comprising the second group of petrosiacetylenes in tropical Petrosia, were isolated from the sponge mentioned directly above (Figure 8) [63].

In the measurement of cytotoxicity against three human cancer cell lines (A2058, H522-T1, H460) and one non-proliferating human fibroblast (IMR-90), all nine compounds (115, 137–144) were active against human cancer cell lines with IC50 values ranging of 0.4–2.7 μM; however, all compounds were also similarly potent against the IMR-90 cells.

In an earlier study on tropical Petrosia sp., aztèquynols A and B (145, 146) were isolated from the cytotoxic extract of a Petrosia sp. collected in New Caledonia [64]. The structures were assigned by NMR spectroscopy, FAB MS/MS, and chemical transformation; however, neither of the compounds accounted for the cytotoxicity of the sponge extract against KB tumor cell lines (less than 20% cytotoxicity at 10 μg/mL).

2.2. Terpenoids and Related Compounds

2.2.1. Sterols Isolated from Tropical Petrosia Sponges

Unique sterols with an extended side chain have been isolated from Petrosia sponges. Sterols were isolated from tropical Petrosia more frequently. There are 12 papers reporting
the isolation of 40 sterols from tropical *Petrosia* sp., while four papers regarding five sterols from temperate counterparts.

**Figure 7.** 2,4-Diyn-1-ols isolated from tropical *Petrosia* sponges.
The first Petrosia-derived sterol was isolated from Indo-Pacific S. durissima [65] (Figure 9). The structure of this sterol (147), named strongylosterol, was completely resolved later by chemical synthesis [66]. Subsequently, additional minor sterols (148–151) were isolated from the extract of the same species, and the structures were elucidated by comparing spectroscopic data with those obtained for synthesized derivatives [67,68].

Oxygenated cholestan derivative were isolated from a Petrosia sp. collected off the Saudi Arabian Red Sea coast (21° N) [69]. The compounds in this series—containing a tetracyclic skeleton of 3,7,9-trihydroxycholestanate (152)—are isolated in the form of oxidized derivatives, i.e., formate (153), epoxide (154), peroxide (155), and diene (156). Compounds with the reduced C-7 (157) or a carbonyl group at C-17 (158) were also isolated. For these compounds, cytotoxicity against human hepatocellular carcinoma (HepG2) and human breast adenocarcinoma (MCF7) was measured; however, none of the compounds showed a meaningful level of activity.

The C29-steroids with a cyclopropane ring at C-25–C-27 (159–174) were isolated from the Thai sponge of Petrosia genus (Figure 10) [70]. Based on the assumption that compounds with 3-dimethyl ketone functionality (161, 162, 169, 170, 172) might have been artificially formed during isolation and purification, compounds with a carbonyl group at C-3 (165, 173) were subjected to conditions similar to those during isolation and purification. No change in the thin layer chromatography analyses was observed, even after one month, suggesting that isolated dimethyl ketone derivatives occur naturally. Compounds—except for 162, 167 and 169—were evaluated for cytotoxicity against six human cancer cell lines and a normal cell line. Compound 173 was the most potent, with IC50 values of 7.1 and 6.1 µM against HepG2 and HeLa cell lines, respectively. All the other compounds exhibited minimal to weak cytotoxicity, with IC50 values in the range of 11.2–103.5 µM.

Xetobergsterol A (175) and contignasterol (176), which contain a highly oxygenated cyclic skeleton and a ketone moiety at C-15, were isolated from P. cf. contignata and P. contignata Thiele, respectively [71,72]. Both compounds contain a 14β hydrogen, which is very rare in naturally occurring steroids, although steroids with a 14β-hydroxyl functionality (i.e., digitoxin) are well-known in nature.

Three pregnane derivatives (177–179) bearing the unique 2,10-carbolactone moieties were isolated from Strongylophora (Petrosia) sp. collected at Puako, Hawaii [73]. The structures were assigned based on spectroscopic data and confirmed by X-ray crystallography of 177. Compounds 178 showed marginal cytotoxicity against human epidermoid carcinoma (KB) and human colorectal adenocarcinoma (LoVo) cell lines with MIC values of 1.0 and 5.0 µg/mL, respectively, while compound 177 and 179 showed no activity.

Sulfated sterols with an ortho ester (orthoesters A–C, 180–182) were isolated from the extract of P. weinbergi collected in the Bahamas (Figure 11) [74]. The compounds were
isolated through the bioassay-guided separation of the extract, which showed activity against feline leukemia virus (FELV), mouse influenza virus (PR8), and mouse coronavirus (A59) and all three (180–182) showed activities against FELV and PR8.

Figure 9. Sterols isolated from tropical Petrosia sponges.

Weinbesterol A and B (183, 184), sulfated tetrahydroxysteroids with a cyclopropane-containing side chain, were isolated from the P. weinbergi collected in the Bahamas [75]. The structures were resolved using extensive NMR experiments, including 2D INADEQUATE, HMBC, HETCOR, COSY, and COLOC. Both were active against FELV (EC50 = 4.0 and 5.2 µg/mL, respectively), and 183 was active against HIV (EC50 = 1.0 µg/mL).

Lembehsterol A and B (185, 186) were isolated from P. strongylata collected at Lembeh Island, Indonesia [76]. Both showed inhibitory activity against thymidine phosphorylase (IC50 = 41.0 and 45.0 µM, respectively) which is related to angiogenesis in solid tumors. Desulfated derivatives obtained by the treatment of 185 with acid showed no inhibition at 230.0 µM, suggesting the importance of the sulfate group for the activity against thymidine phosphorylase.

2.2.2. Sterols Isolated from Temperate Petrosia Sponges

Sterols have rarely been isolated from Petrosia sponges in temperate regions. Only two species, P. ficiformis and S. corticata, were found to contain sterol compounds. All the isolated sterols from both contain cyclopropane in the branch at C-17 (Figure 12). Petrosterol (187), a steroid with a cyclopropane ring at C-25 and C-26, was isolated from P. ficiformis collected in the Bay of Naples, and its structure was confirmed by the X-ray crystallography of a synthesized p-bromobenzoate derivative [77,78]. Subsequent studies tracing the minor component of the same species resulted in the isolation of ficisterol (188) [79]. 7-Oxo and 7-hydroxy derivatives of petrosterol (189, 190) were isolated from S. corticata collected off the coast of Tokushima (33° N) [80] along with petrosterol (187) and
dihydrocalysterol (191). Compound 191 has been isolated from the sponge Calyx niceaensis, previously [81]. The biological activity of the petrosterol analogs (187–191) have not been reported yet.

Figure 10. Polyhydroxysterols isolated from tropical Petrosia sponges.

Figure 11. Sulfated sterols isolated from tropical Petrosia sponges.
Meroterpenoids are a group of compounds that are partially derived from the terpenoid biosynthetic pathway. In the marine environment, meroterpenoids have been isolated most frequently from brown algae and microorganisms, but another important source is marine invertebrates, such as sponges and tunicates [82]. All the meroterpenoids isolated from *Petrosia* sponges are from sponges collected in tropical areas.

Strongylophorines, which are meroditerpenoids with a quinol or a quinone moiety, are the most abundant meroditerpenoids in *Petrosia* sponges (Figure 13). Initially, strongylophorines 1–3 (192–194) were isolated from *S. durissima* collected in Papua New Guinea and identified based on their spectral properties, chemical synthesis, and X-ray diffraction analysis [83]. Five additional analogs, strongylophorines 4–8 (195–199), were isolated from the same species collected in the Philippines [84]. These compounds (192–199) exhibited mild antimicrobial activity against *Bacillus subtilis* and *Staphylococcus aureus*, with the two quinones (197, 198) showing the greatest inhibition. Strongylophorines 9, 11 and 12 (200–202) were isolated from the same species inhabiting Taiwanese water, along with strongylophorine 1–3 (192–194), and 5 (196) [62,85].

Eighteen strongylophorines (192–195, 199, 203–215) were isolated from Okinawan *Petrosia* sponges. From *P. corticata*, strongylophorines 1–4 (192–195), 8 (199), 15–16 (209, 210), and 22–24 (203–205) were isolated and structures were identified by spectroscopic analysis and chemical transformation [86]. Among these compounds, strongylophorine 22 (203) showed moderate cytotoxicity against HeLa cells with an IC\_50 value of 26.6 µM. Eleven derivatives—strongylophorines 2–4 (193–195), 8 (199), 13–19 (207–213)—were isolated from *S. strongylata* [87]. Except for strongylophorine 4 (195), all compounds inhibited the maturation of starfish oocytes with IC\_50 values of 1.1–37.6 µM. The same species inhabiting in the same area were revisited after 10 years, which resulted in the isolation of additional analogs, 214 and 215, the acetal derivatives of strongylophorines [88]. In this study, the inhibitory activity of all the obtained strongylophorines (193, 194, 199, 209, 211, 214, 215) was measured against protein tyrosine phosphatase 1B (PTP1B), which plays a key role in the negative regulation of the insulin and leptin signaling pathways. Most of the compounds showed activity with 214 and 215 being the most potent (IC\_50 8.7 and 8.5 µM, respectively).

Strongylophorines, which are the same as the above mentioned compounds from Okinawan *Petrosia*, were isolated from *P. corticata* collected in North Sulawesi, Indonesia [89]. In this study, the inhibitory activities of the isolated compounds (193–195, 199, 203, 207, 208, 214, 215) were tested against the chymotrypsin-like activity of proteasome. The mixture of diasteromeric hemiacetals (strongylophorines 13, 14; 207, 208) were the most potent (IC\_50 2.1 µM), and the acetal compounds (214, 215) were slightly less potent (IC\_50 9.3 and 6.6 µM, respectively), while the analogous lactone (193) showed no activity at 100 µM. Compounds 194, 195, and 203—bearing a carboxylate, an aldehyde, and a methyl group at C-4, respectively—showed the activities decreased in the same order (IC\_50 9.5, 19.0, 100.0 µM, respectively).
Strongylophorine 26 (216) was isolated from the *P. corticata* collected in Papua New Guinea, along with strongylophorine 8 (199) [90]. Compound 216 exhibited an IC₅₀ value of approximately 1.0 µg/mL in the anti-invasion assay using MDA-231 cells, while 199 showed considerably less potency (IC₅₀ ~7.0 µg/mL).

A dimeric strongylophorine (217), composed of two equivalents of strongylophorine 3 (194), was isolated from a Philippine marine sponge of the genus *Strongylaphora* (*Petrosia*), along with strongylophorines 2–4 (193–195) [91]. In this study, compounds 194 and 195 showed marginal activity against *Micrococcus luteus* and *Salmonella typhi*, respectively. Compound 194 was also active against the phytopathogenic fungus *Cladosporium cucumerinum* and the neonate larvae of the polyphagous insect pest *Spodoptera littoralis* (EC₅₀ 69.0 µg/mL). Compound 217 was the most active in the brine shrimp lethality assay, with an LC₅₀ value of 10.5 g/mL.

Pentacyclic quinones with a furan moiety make up another group of meroditerpenoids from *Petrosia* sponges (Figure 14). Halenaquinone (218), xestoquinone (219), and adociaquinones (220, 221) are representatives of petacyclic quinones, originally isolated from sponges of the genus *Xestospongia* [92,93] or *Adocia* [94] (Schmitz and Bloor 1988).

A series of halenaquinone derivatives—including eight monomers (218, 222–228), six dimers (229–234), and two trimers (235, 236)—were isolated from *P. alfiani* collected in Indonesia (Figures 14 and 15) [95]. The structures were identified based on their NMR spectra, ECD spectra, and DFT calculations. All compounds, except for 222 and 223, were
evaluated for their inhibitory activity against ubiquitin-specific protease 7 (USP7), an enzyme related to the tumor suppression. All tested compounds exhibited potent activities with IC₅₀ values of 0.1–2.0 µM.

![Chemical structures of halenaquinones and xestoquinones.](image)

Figure 14. Monomeric halenaquinone derivatives isolated from tropical *Petrosia* sponges.

The bioassay-guided separation of the extract of *P. alfiani* collected off the coast of Malaysia resulted in the isolation of xestoquinone derivatives (219–221, 237–240) (Figure 14) [96]. The extract selectively inhibited iron chelator-induced hypoxia-inducible factor-1 (HIF-1) in the human breast tumor (T47D) cell-based reporter assay, and adociaquinones A (220) and B (221) were proven to be the active pharmaceutical ingredients (IC₅₀ 0.2 µM against HIF-1). Mechanistic studies revealed that both compounds promote oxygen consumption without affecting mitochondrial membrane potential. In addition, four compounds (219–221, 237) including adociaquinones (220, 221) exhibited potent cytotoxicity (IC₅₀, 2.6–6.5 µM) against two human breast cancer cell lines, T47D and MDA-MB-231, in a cell viability assay.

The dimers of halenaquinol (241, 242) connected through peroxide linkage have been isolated from *P. elastica* collected in Taiwan (Figure 15) [97]. In this study, halenaquinone (218) and halenaquinol could be obtained by degrading 241. The natural dimers (241, 242) exhibited higher growth inhibitory activity compared to the synthesized monomeric counterparts (218, halenaquinol) against human hepatoma cancer cells (Hep3B) at 10.0 µg/mL (5% versus 47% and 20%, respectively).

A sesquiterpene-methylene quinone, puupehenone (243), was isolated from *S. hartmani* van Soest collected in the Bahamas (Figure 16) [98]. This compound was originally reported as a metabolite from a sponge of the genus *Hetronema* [99]. A sesquiterpene hydroquinone, strongylin A (244), was isolated from the same species later [100]. Strongylin A exhibited cytotoxicity against a murine leukemia cell line (P388) and influenza virus (PR8), with IC₅₀ values of 13.0 and 6.5 µg/mL, respectively.

2.2.4. Saponins Isolated from Indonesian *Petrosia* sp.

Lanostane-type triterpene oligoglycosides, sarasinosides (245–248), were isolated from the Indonesian *Petrosia* sponge (Figure 17) [101]. Sarasinosides were originally isolated from marine sponges of the genera *Asteropus*, *Melophlus*, and *Lipastrotethya* [102–104].
which belong to the same subclass (*Heteroscleromorpha*) as *Petrosia*. Compound 245, named sarasinoside S, was isolated for the first time and its structure was elucidated based on its spectroscopic data. None of these isolated sarasinosides exhibited cytotoxicity against human solid cancer cell lines, Huh-7 and A549, although some sarasinoside derivatives have been reported to exhibit weak cytotoxicity against several cancer cell lines.

![Figure 15](image)

**Figure 15.** Dimeric and trimeric halenquinone derivatives isolated from tropical *Petrosia* sponges.

![Figure 16](image)

**Figure 16.** Merosesquiterpenoids isolated from *S. hartmani*.

2.3. **Alkaloids and Peptides**

2.3.1. Alkaloids Isolated from Tropical *Petrosia* Sponges

Several alkaloids have been isolated from *Petrosia* sponges inhabiting tropical regions, whereas no alkaloids from the temperate *Petrosia* have been reported. Petrosin
(249), a bisquinolizidine isolated from *P. seriata* collected in Papua New Guinea, is the first reported *Petrosia*-derived alkaloid (Figure 18) [105].

![Figure 17. Saponins isolated from an Indonesian *Petrosia* sp.](image1)

![Figure 18. Alkaloids isolated from tropical *Petrosia* sponges.](image2)
Isoquinoline alkaloids have been isolated from Petrosia sponges. Mimosamycin (250) and related derivatives (251–254) were isolated from Petrosia sp. and P. similis collected in India [106,107]. Isoquinoline quinones analogous to 254 (255–257) were isolated from two Philippine Petrosia sponges [108]. These compounds exhibited low cytotoxicity with an IC₅₀ ranging from 24.0 to 45.0 µg/mL against the HCT116 human colon carcinoma cell line.

Petrosamine (258), a pyridoacridine alkaloid, was isolated from the Petrosia sp. collected in Belize [109]; it was confirmed to exist as a keto form by X-ray crystallography. However, a signal corresponding to that of a C-5 carbonyl group (δc 161 ppm) was detected, which suggests that it takes an enol form in solution. 2-Bromoamphimedine (259) was isolated later from a Thai marine sponge along with 258 [110]. Compound 258 showed strong acetylcholinesterase inhibitory activity approximately six times higher than that of galantamine that used as a reference (IC₅₀ 0.09 vs. 0.59 µM), while 259 was totally inactive.

Purine derivatives (260–263) conjugated with a β-amino acid were isolated from P. nigricans collected in Indonesia, and named nigrines [111]. None of these compounds showed cytotoxicity against the murine lymphoma cell line (L5178Y) at 10.0 µg/mL, and no other activities could be measured due to the limited quantities obtained.

Phenethylguanidine alkaloids isolated from Indo-Pacific marine sponge P. cf. contigua, (264, 265) are close derivatives of tubastrine [71]. Tubastrine was originally reported as a metabolite of the soft coral Tubastrea aurea, and compound 264 has previously been synthesized by the hydrogenation of tubastrine [112].

2.3.2. Peptides Isolated from a Korean Petrosia sp.

So far, only one article has reported the isolation of peptides from Petrosia sponge. This article described the isolation of five halicylindramides (266–270) from the Petrosia sp. collected in Korea (Figure 19) [113]. The structures of newly reported compounds (268–270) were elucidated based on their spectroscopic and mass data, and the stereochemistry was assigned by Marley’s method and ECD spectroscopy. The article points out that the producers of these compounds might be sponge-associated cyanobacteria, as all of the previously reported halicylindramides were discovered from the sponge Halichondria cylindrata. Compounds 266–268, bearing indole moiety at R₁ position, showed antagonistic activity against human farnesoid X receptor (hFXR) with IC₅₀ values of 6.0, 0.5, and 5.0 µM, respectively, while 269 and 270 were inactive even at 100.0 µM.

![Figure 19. Depsipeptides isolated from a Korean Petrosia sp.](image-url)

2.4. Fatty Acid Derivatives

A cyclitol derivative (271) was reported as a metabolite of Korean Petrosia sp. (Figure 20) [114]. This compound exhibited minimal cytotoxicity against a panel of human solid tumor cells with IC₅₀ values around 10.0 µg/mL; however, HeLa extract-promoted in vitro DNA replication was inhibited by the treatment of 271 in a dose-dependent manner.
Sphingolipid 272 was isolated from Red Sea Petrosia sp. and exhibited minimal cytotoxicity against MCF-7 and HepG2 cell lines with IC₅₀ values around 20.0 µg/mL [69]. Brominated fatty acids (273–277) were isolated from the Caribbean Petrosia sp., and its structure was elucidated by mass spectrometry and chemical transformations, including deuteration with Wilkinson’s catalyst [115].

**Figure 20.** Fatty acid derivatives isolated from Petrosia sponges.

### 3. Discussion

This review addressed 277 compounds isolated from Petrosia sponges from 87 peer-reviewed articles (Figure 21). The type of predominant metabolite depended on the geographical location of the source sponge. Polyacetylenes were the most frequently found in Petrosia sponges inhabiting temperate regions. Of the 36 research articles regarding the metabolites isolated from sponges collected in the Mediterranean Sea, Korean waters, or the temperate regions of Japan, 29 reported the isolation of polyacetylenes. More than 100 polycyclacetylenes have been isolated from temperate Petrosia sponges, and 44 polycyclacetylenes were reported as the metabolites of tropical Petrosia sponges.

**Figure 21.** Number of compounds and publications for each type of Petrosia metabolites.

Meroterpenoids and sterols were the most frequently found metabolites in tropical Petrosia sponges; 15 and 12 articles of the 50 papers on the metabolites of tropical Petrosia sponges.
sponges report a total of 53 meroterpenoids and 40 steroids, respectively. There are only five reported sterols isolated from *Petrosia* collected in Italy and Japan, and no reported meroterpenoids have been isolated from temperate *Petrosia* sponges. Alkaloids have also only been isolated from tropical *Petrosia* sponges. Seventeen alkaloids have been reported in eight publications regarding the *Petrosia* sponges collected in the Philippines, Indonesia, Papua-New Guinea, India, Belize, and Saudi Arabia.

Saponins and peptides have also been isolated from *Petrosia* sponges, but they are not very common. Four noriterpene glycosides of the sarasinoside class were isolated from the Indonesian *Petrosia* sp., and five depsipeptides were isolated from a Korean *Petrosia* sponge. Considering the scarcity of these compounds, their origins might be the sponge-associated microbes.

All metabolites isolated from *Petrosia* sponges from temperate and tropical regions are summarized in Table 1 and Table 2, respectively.

| Compound | Examined Biological Activity | Species | Reference |
|----------|-----------------------------|---------|-----------|
| **Polyacetylenes** |                             |         |           |
| **petroformynes** |                             |         |           |
| 1–4      | toxicity (fertilized sea urchin eggs, *A. salina*) | *P. ficiformis* | [28,29] |
| 1–15, 18–20, 22–24 | brine shrimp lethality | *P. ficiformis* | [30,31] |
| 16, 17, 21, 25 | not reported | *P. ficiformis* | [32] |
| **petrosynol and petrosyne** |                             |         |           |
| 26, 27   | toxicity (fertilized sea urchin eggs) | *Petrosia sp.* | [33,34] |
| 28–31    | toxicity (fertilized ascidian eggs), brine shrimp lethality | *Petrosia sp.* | [35] |
| **petroacetylene** |                             |         |           |
| 32       | inhibition of the blastulation of starfish embryo | *Petrosia sp.* | [36] |
| **petroformynes and neopetroformynes** |                             |         |           |
| 1, 4, 33–36 | cytotoxicity (P388) | *Petrosia sp.* | [38] |
| **durynes and miyakosynes** |                             |         |           |
| 37–42    | cytotoxicity (HeLa) | *Petrosia sp.* | [39] |
| 43–48    | cytotoxicity (HeLa) | *Petrosia sp.* | [42] |
| **petrosynes** |                             |         |           |
| 49–50    | not reported | *Petrosia sp.* | [43] |
| **corticatic acids** |                             |         |           |
| 51–53    | antifungal activity (*M. ramanniana*) | *P. corticata* | [44] |
| 54–55    | inhibition of GGTase I from *C. albicans* | *P. corticata* | [45] |
| **petroformynes and petroformynic acids** |                             |         |           |
| 1, 4, 56, 57 | cytotoxicity (P388) | *P. corticata* | [37] |
| **petrocortynes and petrosiacetylenes** |                             |         |           |
| 58–60, 84–87 | brine shrimp lethality, RNA-cleaving activity | *Petrosia sp.* | [46] |
| 61–65    | cytotoxicity (K562) | *Petrosia sp.* | [47] |
| 66–83, 89, 90 | cytotoxicity (*A549, SK-OV-3, SK-MEL-2, XF498, HCT-15*) | *Petrosia sp.* | [48–51] |
| 84–86, 88 | cytotoxicity (*A549, SK-OV-3, SK-MEL-2, XF498, HCT-15*) | *Petrosia sp.* | [52] |
| 84–86, 91 | cytotoxicity (*NCI-H23, PC-3, ACHN, NUGC-3, HCT-15*) | *Petrosia sp.* | [53] |
| **petroraspailynes, raspailynes and petrosynol** |                             |         |           |
| 92–102   | cytotoxicity (K562) | *Petrosia sp.* | [54] |
| **Sterols** |                             |         |           |
| 187–188  | not reported | *P. ficiformis* | [77–79] |
| 187–191  | not reported | *P. corticata* | [80] |
| **Peptides** |                             |         |           |
| **halicylindramides** |                             |         |           |
Table 2. Metabolites isolated from *Petrosia* sponges in tropical region.

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| **Fatty acid derivatives**    |                                                                    |                |           |
| 266–270                       | antagonistic activity against human farnesoid X receptor          | *Petrosia* sp. | [113]     |
| **Saponins**                  |                                                                    |                |           |
| 271                           | cytotoxicity (A549, SK-OC-3, SK-MEL-2, XF498, HCT-15)              | *Petrosia* sp. | [114]     |
| 272                           | cytotoxicity (MCF7, HepG2)                                        | *Petrosia* sp. | [69]      |
| **Meroterpenoids**            |                                                                    |                |           |
| 28                            | inhibition of the maturation of starfish oocytes                  | *P. strongylata* |          |
| 192–194                       | inhibition of protein tyrosine phosphatase 1B                     | *P. strongylata* |          |
| 193–195, 199, 203, 207–213    | inhibition of thymidine phosphorylase                             | *P. corticata* |          |
| 193, 194, 199, 209, 211, 214, 215 | inhibition of protein tyrosine phosphatase 1B                    | *P. strongylata* |          |
| 193, 194, 199, 203, 207, 208, 214, 215 | chymotrypsin-like activity of proteasome                        | *P. corticata* |          |
| 192–195, 199, 203, 207, 208, 214, 215 | inhibition of thymidine phosphorylase                             | *P. corticata* |          |

**Table 2. Metabolites isolated from *Petrosia* sponges in tropical region.**

*Polyacetylenes*

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 103–105                       | cytotoxicity (MOLT-4, IMR-90, DLD-1)                              | *Petrosia* sp. | [56]      |
| 106–112                       | not reported                                                      | *Petrosia* sp. | [57]      |

**Strongylodiols and pellynols**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 113–117                       | cytotoxicity (HeLa, K-562)                                        | *Petrosia* sp. | [58]      |

**Strongylodiols and petrosiols**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 105, 106, 118–122             | induction of neuronal differentiation (PC-12)                    | *P. strongylata* | [59]      |
| 123–131                       | not reported                                                      | *P. durissima* | [61]      |
| 132–136                       | cytotoxicity (NUGC)                                               | *P. durissima* | [62]      |

**Pellynols and petrosiolic acids**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 115, 137–144                  | cytotoxicity (A2058, H522-T1, H460, IMR-90)                       | *Petrosia* sp. | [63]      |
| 145–146                       | cytotoxicity (KB)                                                 | *Petrosia* sp. | [64]      |

**Sterols**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 147                           | not reported                                                      | *P. durissima* | [65,66]   |
| 148–151                       | not reported                                                      | *P. durissima* | [67,68]   |
| 152–158                       | cytotoxicity (HepG2, MCF7)                                        | *Petrosia* sp. | [69]      |
| 159–174                       | cytotoxicity (MOLT-3, HepG2, A549, HuCCA-1, HeLa, MDA-MB-231, MRC-5) | *Petrosia* sp. | [70]      |

**Xestobergsterol A**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 175                           | not reported                                                      | *P. cf. cotignata* | [71]     |
| 176                           | cotignasterol                                                     | *P. cotignata* | [72]      |
| 177–179                       | cytotoxicity (KB, LoVo)                                           | *Petrosia* sp. | [73]      |

**Orthosterols**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 180–182                       | antiviral activity (FELV, PR8, A59)                               | *P. weinbergi* | [74]      |
| 183, 184                      | antiviral activity (FELV, HIV)                                    | *P. weinbergi* | [75]      |

**Weinbersterols**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 185, 186                      | inhibition of thymidine phosphorylase                             | *P. strongylata* | [76]      |

**Meroterpenoids**

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
| 192–194                       | antimicrobial activity (*B. subtilis, S. aureus*)                | *P. durissima* | [83]      |
| 195–199                       | antimicrobial activity (*B. subtilis, S. aureus*)                | *P. durissima* | [84]      |
| 192–194, 196, 200–202         | cytotoxicity (NUGC)                                              | *P. durissima* | [62,85]   |
| 192–195, 199, 203–205, 209, 210 | cytotoxicity (HeLa)                                             | *P. corticata* | [86]      |
| 193–195, 199, 207–213         | inhibition of the maturation of starfish oocytes                 | *P. strongylata* | [87]      |
| 193, 194, 199, 209, 211, 214, 215 | inhibition of protein tyrosine phosphatase 1B                    | *P. strongylata* | [88]      |
| 193–195, 199, 203, 207, 208, 214, 215 | chymotrypsin-like activity of proteasome                        | *P. corticata* | [89]      |

| Compound                      | Examined Biological Activity                                      | Species        | Reference |
|-------------------------------|-------------------------------------------------------------------|----------------|-----------|
Considering that the actual producers of natural products isolated from sponges are the microbes associated therein in many cases [8,10], the latitudinal variation in metabolite composition of *Petrosia* sponges might be correlated with their associated microbial community. Genes involved in the biosynthesis of *Petrosia* metabolites have never been deduced until now; however, the biosynthetic gene clusters for analogous polyacetylenes, meroterpenoids, and terpenoids have been found from fungi, cyanobacteria, and actinomycetes. In addition, it has been reported for *P. ficiformis* that microbial symbiotic populations were more similar in genetically distinct individuals from the same location, than in genetically similar individuals from distant regions [116]. The factors which affects the structure of associated microbial community might be diverse and complex, as tropical and temperate seas have completely different ecosystems, not to mention physical factors, such as temperature and salinity. To better understand the factors that govern the composition of sponge metabolites, research to analyze the structure of associated microbial community of the sponges using various metagenomics tools should be conducted.

The biological activity most frequently investigated for *Petrosia* metabolites was cytotoxicity; most of the petrosiacetylenes showed growth inhibitory activity against human cancer cell lines. Research to better understand the ecological and pharmacological role of these compounds should be conducted. Biogenesis of *Petrosia* metabolites would be another significant topic in this field. This research would reveal the symbiotic relationships between marine sponges and microorganisms, and the strategies in biosynthesis that can be applied to the production of biologically-relevant molecules. In addition, the discovery

| 199, 216 | cytotoxicity (MDA-231) | *P. corticata* [90] |
| 193–195, 217 | antimicrobial activity (*M. lueus, S. typhi, C. cucumerrnum*), brine shrimp lethality | *Petrosia* sp. [91] |
| 218, 222–236 | inhibition of ubiquitin-specific protease 7 | *P. alfianni* [95] |
| 219–221, 237–240 | inhibition of iron chelator-induced HIF-1, cytotoxicity (T47D, MDA-MB-231) | *P. alfianni* [96] |

| dihalenaquinolides | 241, 242 | cytotoxicity (Hep3B) | *P. elastica* [97] |
| puupehenone | 243 | cytotoxicity (P388, A549, MCF7) | *P. hartmani* [98] |
| strongylin A | 244 | cytotoxicity (P388), antiviral activity (PR8) | *P. hartmani* [100] |

| Saponins | sarasinositides | Cytotoxicity (Huh-7, A549) | *Petrosia* sp. [101] |
| Alkaloids | petrosin | 249 | not reported | *P. seriata* [105] |
| | 250–253 | not reported | *Petrosia* sp. [106] |
| | 254 | not reported | *P. similis* [107] |
| | 255–257 | cytotoxicity (HCT116) | *Petrosia* sp. [108] |
| petrosamine | 258 | not reported | *Petrosia* sp. [109] |
| | 258, 259 | inhibition of acetylcholinesterase | *Petrosia* sp. [110] |

| Nigrlines | 260–263 | cytotoxicity (L5178Y) | *P. nigricans* [111] |
| | 264, 265 | not reported | *P. cf. contignata* [71] |

| Fatty acid derivatives | 273–277 | not reported | *Petrosia* sp. [115] |
of novel genes involved in the biosynthesis would provide potential bioengineering applications.

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