marine drugs

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Review

Chemical Diversity and Biological Activities of Marine Sponges of the Genus *Suberea*: A Systematic Review

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Abstract: Marine natural products (MNPs) continue to be in the spotlight in the global drug discovery endeavor. Currently, more than 30,000 structurally diverse secondary metabolites from marine sources have been isolated, making MNPs a profound, renewable source to investigate novel drug compounds. Marine sponges of the genus *Suberea* (family: Aplysinellidae) are recognized as producers of bromotyrosine derivatives, which are considered distinct chemotaxonomic markers for the marine sponges belonging to the order Verongida. This class of compounds exhibits structural diversity, ranging from simple monomeric molecules to more complex molecular scaffolds, displaying a myriad of biological and pharmacological potentialities. In this review, a comprehensive literature survey covering the period of 1998–2018, focusing on the chemistry and biological/pharmacological activities of marine natural products from marine sponges of the genus *Suberea*, with special attention to the biogenesis of the different skeletons of halogenated compounds, is presented.

Keywords: marine sponges; Verongida; *Suberea*; bromotyrosine derivatives; bioactivities; biosynthesis

1. Introduction

Oceans occupy almost 70% of the Earth's surface, furnishing extraordinary biological and chemical diversity in different ecosystems on our planet [1]. Marine natural products (MNPs) have displayed a distinct track record as a rich and renewable source for novel drug leads [2]. Indeed, the majority of the newly discovered pharmacophores with potent biological/pharmacological activities are derived from marine sponges, corals, and tunicates, among other marine invertebrates [3]. Marine sponges (phylum: Porifera) are a large class within the animal Kingdom, and are considered prolific factories for producing bioactive natural products [4–7]. Currently, many MNPs and their derivatives are among the approved drugs on the market. These include anticancer drugs such as cytarabine (Cytosar-U®, DepoCyst®: FDA approval in 1969 for cancer), vidarabine (Vira-A®, approved by FDA in 1976 as an antiviral), trabectedin (Yondelis®, ET- 743, EU approval in 2011 for cancer), eribulin mesylate (Halaven®, FDA approval in 2010, and Heath Canada approval in 2011 for metastatic breast cancer), and brentuximab vidotin (Adcetris®, FDA approval in 2011 for Hodgkin's lymphoma and in 2017 for cutaneous T-cell lymphoma), and other drugs such as ziconotide (Prialt®, approved by FDA in in 2004 as an analgesic for treatment of severe chronic pain) and ω-3 acid ethyl esters (Lovaza®, approved by FDA in 2004 for lowering blood triglyceride levels in adults with severe hypertriglyceridemia) [8–10]. Furthermore, more than twelve marine-derived compounds are currently under investigation in different clinical phases [2,8–10].

Suberea Bergquist, 1995 [11] is a genus of keratose (or horny) sponges that lacks a mineral skeleton, belonging to the Order Verongida (Family: Aplysinellidae). Species of *Suberea* have smooth or conulose surfaces and can be massive, stalked, or have branching growth forms. Their live coloration is usually bright and vivid (e.g., yellow, orange, brown, or red), with aerophobic pigments that darken when exposed to air. They have thick spongin fibers that form an irregular dendritic skeleton composed of both bark (external) and pith (central) fiber components, with the latter predominating. The bark component of the fibers is strongly laminated, which makes the fibers brittle. In addition, a dense, collagenous mesohyle between the fibers makes these sponges hard and barely compressible [11,12]. The World Porifera Database indicated that the genus *Suberea* currently contains 14 described species with *Suberea* Bergquist, 1995, including: *S. azteca* [13]; *S. clavata* [14]; *S. creba* [11]; *S. elegans* [15]; *S. etiennei* van Soest, Kaiser & Van Syoc, 2011 [16]; *S. flavolivescens* [17]; *S. fusca* [18]; *S. ianthelliformis* [15]; *S. laboutei* Bergquist [11]; *S. meandrina* [19]; *S. mollis* [20]; *S. pedunculata* [21]; *S. praetensa* [20]; and *S. purpureaflava* Gugel, Wagler & Brümmer, 2011 [22]. Sponges of the genus *Suberea* are found in shallow waters at depths from 8 to 55 meters, in both warm temperate and tropical waters off the coasts of Victoria, New South Wales, the Great Barrier Reef, Northwest Australia, Aru & Ki Islands, Indonesia, New Caledonia, Kermadec Islands, New Zealand, the Tropical Pacific Mexico, Clipperton Island in the Eastern Pacific, Caribbean Columbia, Gulf of Manaar, Sri Lanka, Southern India, Red Sea (Sudan and Egypt), Persian Gulf, Vema Seamount, and South Africa [23]. A common Indo-Pacific species, *S. ianthelliformis* (Lendenfeld, 1888), has a wide distribution over French Polynesia (Society, Marquesas, Tuamotu Archipelago Islands), Fiji, Solomon Islands, Northeast and Northwest Australia, the Philippines, South China Sea, Malaysia, and Indian Ocean Western Australia [24]. Like other marine sponge genera belonging to the order Verongida (Family: Aplysinellidae), such as *Aplysinella* and *Porphyria*, members of the genus *Suberea* are known to produce diverse structures of brominated tyrosine alkaloids [25,26] that display a myriad of bioactivities (Table 1) including cytotoxicity [27], antimicrobial properties [28], antibacterial properties [29], kinase inhibitor production [27], and antiproliferative properties [30]. Interestingly, a recent paper by Nicacio et al. [31] reported that a culture of the marine bacterium *Pseudovibrio denitrificans* Ab134, isolated from the Haplosclerida sponge *Arenosclera brasiliensis*, was able to produce bromotyrosine-derived alkaloids. This observation highlights important questions about the discretion in considering these brominated secondary metabolites as chemical markers of the order Verongida, and for marine sponge phylogeny in general. To the best of our knowledge, previous chemical investigations were mainly focused on only six species: *Suberea* sp., *S.* aff. *praetensa*, *S. mollis*, *S. creba*, *S. ianthelliformis*, and *S. clavata*.

As a part of our ongoing research on biologically active marine natural products [32–37], this review comprehensively covers chemistry and biological activities of the isolated secondary metabolites from the marine sponges of the genus *Suberea,* reported over the period of 1998–2018**,** with a special attention to the halogenated compounds and their biosynthetic pathways.

2. Chemistry and Biological Activities of Secondary Metabolites Isolated from the Members of the genus *suberea.*

2.1. Halogenated Tyrosine Derivatives (Isoxazolines, Oxepinisoxazolines, and Phenolics)

From Figure 1—seven cytotoxic bromotyrosine alkaloids, namely ma'edamines A and B (**1** and **2**) that possess a unique 2(*1H*) pyrazinone motif, along with aplysamine-2 (**3**), purpureamines H and I (**4** and **5**), and suberedamines A and B (**6** and **7**) were isolated from an Okinawan *Suberea* sp. [38]. Biosynthetically, **6** and **7**, which are precursors of **1** and **2**, could be formed by the condensation of two bromotyrosine units. Compounds **1** and **2** displayed in vitro cytotoxicity against murine leukemia L1210 and KB (mouth epidermoid carcinoma) cells, with IC_{50} values of 4.3, 3.9, 5.2 and 4.5 μg/mL, respectively. Furthermore, these compounds also exhibited inhibitory activity against c-erbB-2 kinase, with IC_{50} values of 6.7 and >10 μg/mL, respectively. Similarly, **6** and **7** exhibited in vitro cytotoxicity against murine leukemia L1201, with IC_{50} values of 8.0 and 8.6 μg/mL, and also against epidermoid carcinoma KB cells, with IC_{50} values of 9.0 and >10.0 μg/mL, respectively. Compounds **6** and **7** also showed antibacterial activity against *Micrococcus luteus*, with an MIC value of 12.6 μg/mL [27,38]. Furthermore, simple bromotyrosine derivatives isolated from *Suberea* sp., including subereaphenol K (**8**) and 2-(3,5-dibromo-1-ethoxy-4-oxocyclohexa-2,5-dien-1-yl) acetamide (**9**), showed cytotoxicity against NIH-3T3 (mouse embryonic fibroblast), HepG2 (human liver cancer), and HT-29 (human colon adenocarcinoma) cell lines [39]. Interestingly, psammaplysins I (**10**), J (**11**), A (**12**), B (**13**), and F (**14**), which all possess a complex spiro-oxepinisoxazoline scaffold, were also isolated from *Suberea* sp. [40] (Figure 1).

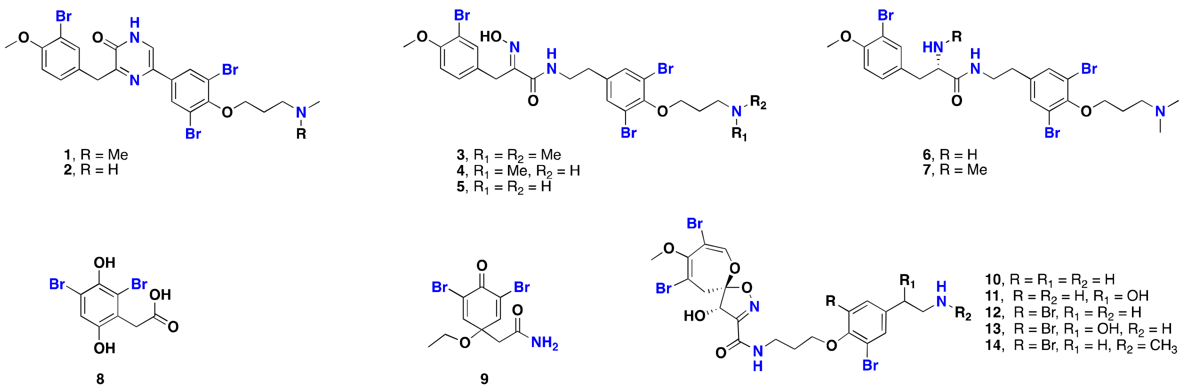

Figure 1. Chemical structures of **1–14.**

From Figure 2—three complex hexabromotyrosine derivatives containing the oxazolidone moiety, namely fistularin-3 (**15**) and 11,17-dideoxyagelorins A (**16**) and B (**17**), along with 5-chlorocavernicolin (**18**), 5-bromocavernicolin (**19**), cavernicolin-1 (**20**), cavernicolin-2 (**21**), subereatensin (**22**), 2-(3′,5′-dibromo-4′-hydroxyphenyl)acetamide (**23**), 3,5-dibromoverongiaquinol (**24**), and *bis*-oxazolidone (**25**) and its acetate congeners (**26** and **27**) were reported from the marine sponge *S*. aff. *praetensa* collected from the Gulf of Thailand [41–43]. Some of these compounds exhibited potent cytotoxicity against five human cancer cell lines: MCF-7 (breast cancer), NCI-H460 (human non-small cell lung cancer), SF268 (glioblastoma), TK-10 (human renal carcinoma), and UACC-62 (human melanoma), with GI_{50} values in the micromolar range [41–43]. Moreover, **15,** which was also isolated from *Alisina archeri*, was shown to inhibit the growth of feline leukemia virus [44]. In addition to antitumor activity, **24** also displayed antibacterial activity [45]. Debitus et al. [46] found that **24,** isolated from *S. creba*, also exhibited a chloramphenicol antibiotic-like activity (quorum sensing inhibition) against the marine bacterium *Vibrio scala*. Weiss et al. [47] described the isolation of **24** from the marine sponge *Verongia aerophoba* and its antibacterial activity against eight different Gram-positive or Gram-negative marine bacteria, including *Alteromonas*, *Moraxella*, and *Vibrio* sp., in addition to potent activity against the marine bacterium *Photobacterium phosphoreum*, with an EC_{50} value of 3.45 μM. Moreover, this compound also inhibited the growth of the marine microalgae *Coscinodiscus wailesii* and *Prorocentrum minimum*, with an EC_{50} of 5.6 μM [47] (Figure 2).

From Figure 3—six cytotoxic and antimicrobial dibromophenol derivatives, including subereaphenol A (**28**), 2-(3′,5′-dibromo-2′-hydroxy-4′-methoxyphenyl) acetamide (**29**), subereaphenol C (**30**), dibromoverongiaquinol (**31**), and bromochloroverongiaquinol (**32**), were isolated from *S. creba* [46], whereas **32** and 2-(3′,5′-dibromo-4′-ethoxy-1′-hydroxy-4′methoxy-2′,5′-cyclohexadien-1-yl) acetamide (**33**) were isolated from *S. mollis*, which was collected from the Egyptian Red Sea [48]. Compound **32** showed antibacterial activity against both Gram-positive (*Sarcina lutea*) and Gram-negative (*Alcaligena faecalis* and *Proteus vulgaris*) bacteria [49]. Compounds **23** and **30–32** [46] were re-isolated from *Suberea* sp., also collected from the Red Sea [50]. Compounds **23**, **30** and **32** exhibited cytotoxic and antiproliferative effects against HCT-116 (human colon cancer) and HeLa (human carcinoma) cell lines, and **32** was found to be the most cytotoxic, with IC_{50} values of 4.5 and 10 μg/mL, respectively. Additionally, **32** also exhibited moderate antibacterial activity against *Escherichia coli*, with an inhibition zone of 12 mm [50].

The oxazolidone-containing metabolites subereamollines A (**34**) and B (**35**), aerothionin (**36**), homoaerothionin (**37**), 11,19-dideoxyfistularin-3 (**38**), and (+)-aeroplysinin-1 (**39**) were reported from *S. creba* [46]. While **36** displayed a feed chemical defense role against the predatory fish *Blennius sphinx* [51], **39** displayed potent antibacterial activity against *Staphylococcus albus*, *Bacillus cereus*, and *B. subtilis*, with MIC values of 20–100 μg/mL [52,53], as well as cytotoxicity against a panel of tumor cell lines, including human cervix uteri, Ehrlich ascites tumor (EAT), and HeLa cell lines [54–57]. Moreover, synthetic congeners of (+)-aeroplysinin-1 showed an in vivo inhibition of the receptor tyrosine kinase (RTK) and antiproliferative activity [58]. Aeroplysinin-2 (**40**) and subereaphenol B (**41**), previously reported from the Red Sea *Suberea* sp. [30], were re-isolated from *S. mollis* also collected from the Red Sea [59] (Figure 3).

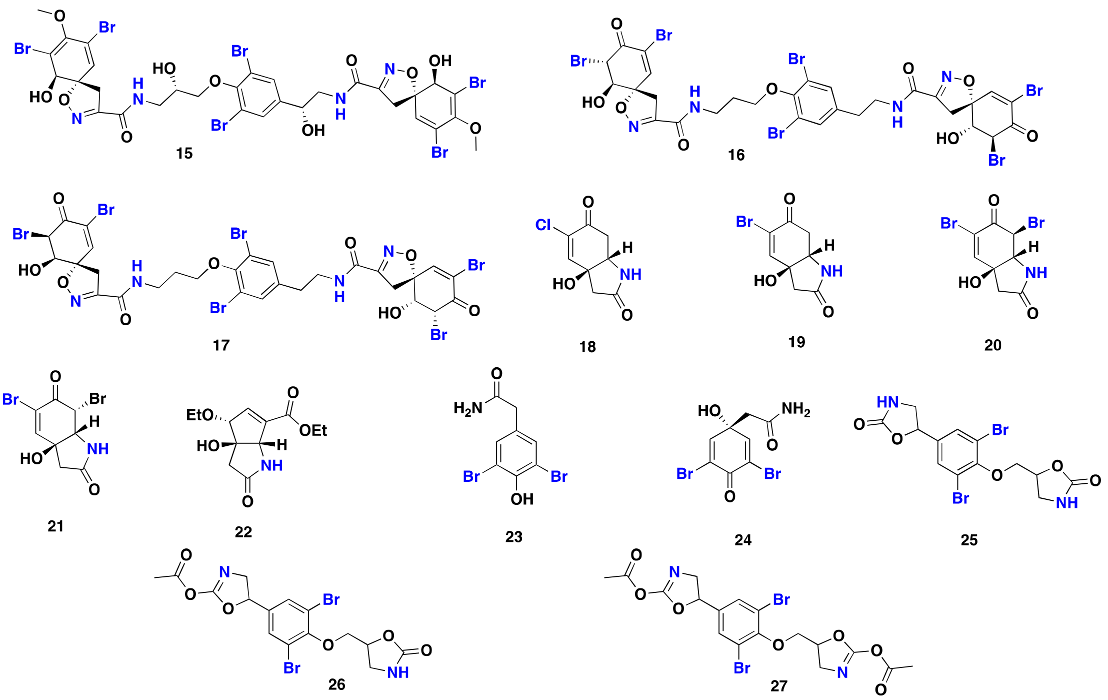

Figure 2. Chemical structures of **15–27.**

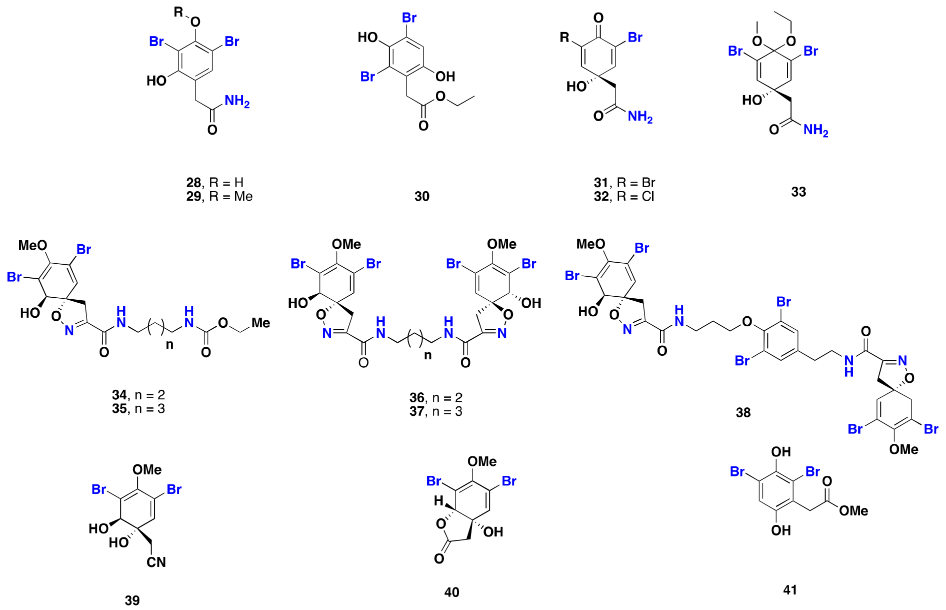

Figure 3. Chemical structures of **28–41.**

From Figure 4—two antimicrobial brominated arginine derivatives, subereamines A and B (**42** and **43**), along with subereaphenol D (**44**), were isolated from *S. mollis* collected in the Egyptian Red Sea [28]. The chemical investigation of *S. clavata* extracts furnished eight guanidine-containing bromotyrosine derivatives, namely clavatadines A–E (**45–49**), aerophobin-1 (**50**), purealidin L (**51**), and aplysinamisine II (**52**) that showed inhibition against Factor XIa [60,61]. The antibacterial bromotyrosine alkaloids possessing polyamine motifs, ianthelliformisamines A–C (**53–55**), were isolated from *S. ianthelliformis* along with aplysamine-1 (**56**) and araplysillin-I (**57**). Compound **53** showed antibacterial activity against the Gram-negative bacterium *Pseudomonas aeruginosa*, with an IC_{50} of 6.8 μM [29] (Figure 4).

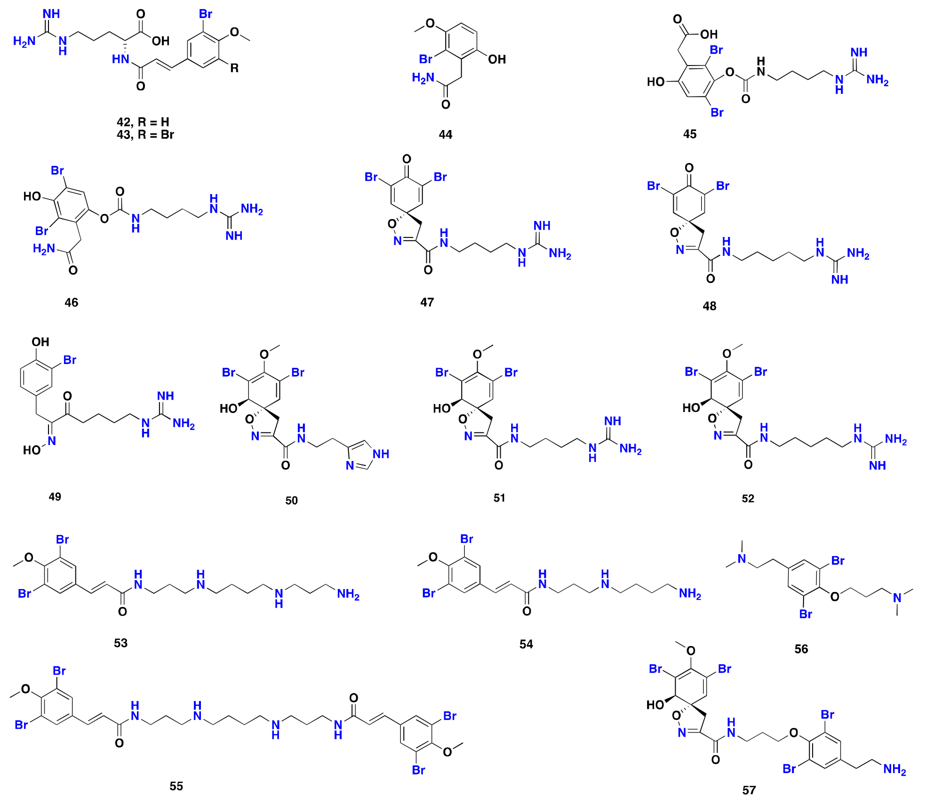

Figure 4. Chemical structures of **42–57**.

From Figure 5—five antiplasmodial metabolites, including araplysillin *N*-20-formamide (**58**), araplysillin *N*-20-hydroxyformamide (**59**), araplysillin IV (**60**), araplysillin V (**61**), and araplysillin VI (**62**), were reported from *S. ianthelliformis*. Compounds **58–62** exhibited weak to moderate inhibitory activities against both chloroquine-resistant and chloroquine-sensitive *Plasmodium falciparum* strains FcB-1 and 3D7, with IC_{50} values in the range of 1.0 to 59 µM, and 0.9 to 19.9 µM, respectively [62]. Subereamollines C and D (**63** and **64**), isolated from *Suberea* sp. collected from the Red Sea, displayed weak antiproliferative activity [30]. Psammaplysins A (**65**), B (**66**), D (**67**), E (**68**), 19-hydoxypsammaplysin E (**69**), psammaplysin X (**70**), 19-hydroxypsammaplysin X (**71**), psammaplysin Y (**72**), 19-hydroxyceratinamide A (**73**), subereamides A–C (**74–76**), and 12-hydroxysubereamide C (**77**), in addition to moloka'iamine (**78**), hyroxymoloka'iamine (**79**), ceratinamine (**80**) and hydroxyceratinamine (**81**), were isolated from a Micronesian sponge *Suberea* sp. These psammaplysin analogues (**65–81**) displayed potent cytotoxicity against six human tumor cell lines, namely HCT-15 (colon cancer), PC-3 (prostate cancer), ACHN (renal cancer), MDA-MB-231 (breast cancer), NUGC-3 (stomach cancer), and NCI-H23 (lung cancer), with GI_{50} values as low as 0.8 µM. This suggests these compounds could serve as promising molecular templates for the development of anticancer agents [63] (Figure 5).

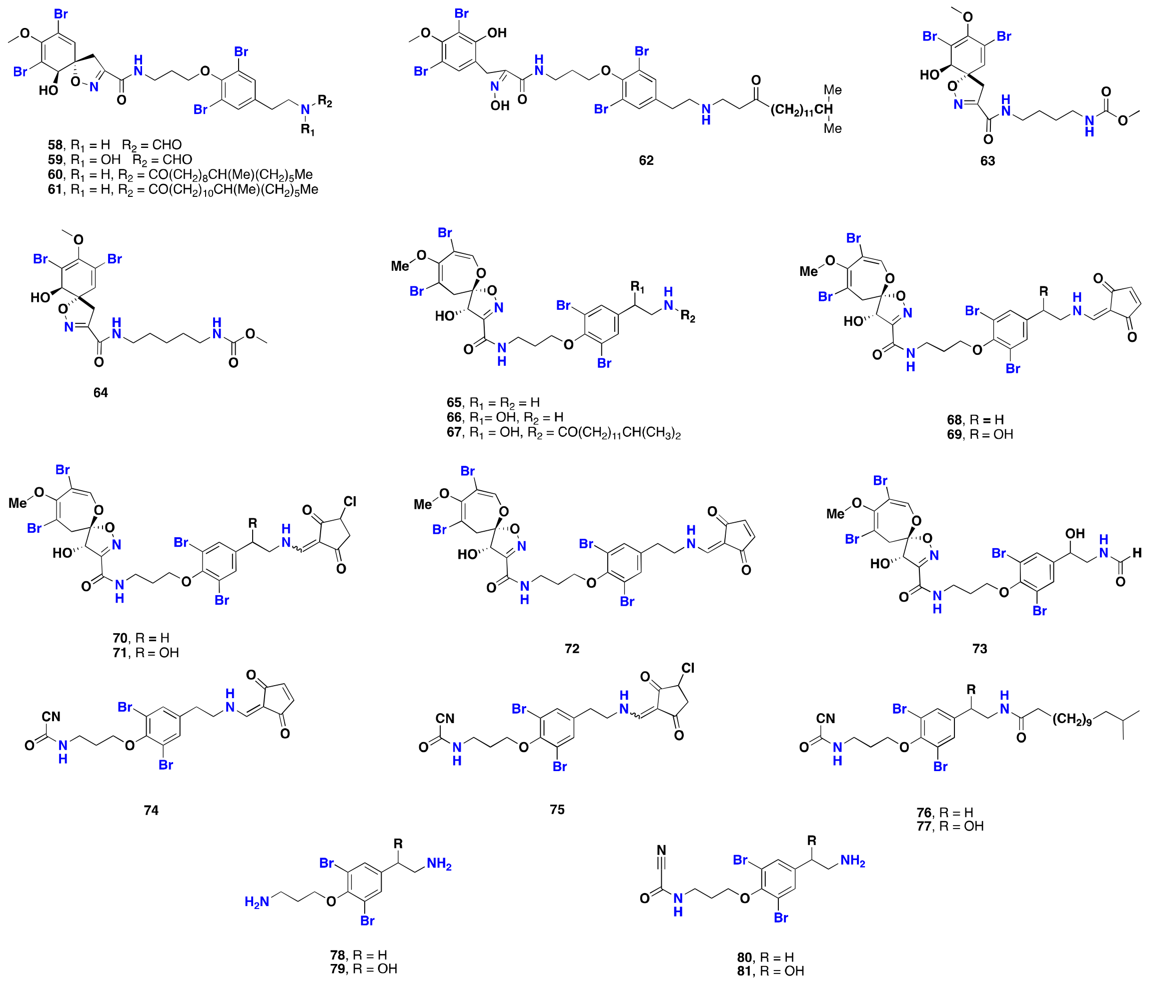

Figure 5. Chemical structures of **58**–**81**.

From Figure 6—Al-Mourabit et al. [64] reported the isolation of eight tetrabromotyrosine alkaloids, psammaplysenes F–I (**82–85**), and anomoians C–F (**86–89**), along with the known natural products psammaplysene D (**90**) and *N,N*-dimethyldibromotyramine (**91**), from the Polynesian sponge *S. ianthelliformis*. Compounds **82, 83** and **86–89** exhibited moderate cytotoxicity against the KB cell line, whereas **90** was the most potent with an IC_{50} of 0.7 µM. Although the structures of **88** and **89** resemble that of **90**, they exhibited weaker cytotoxicity than **90**. It can be hypothesized that the presence of the double bond in the 3,5-dibromo *p*-hydroxycinnamoyl moiety in **90**, instead of the amino or alkylamino group on the carbon adjacent to the amide carbonyl in **88** and **89**, was essential for this activity. Curiously, **82**, which contains a double bond in the 3,5-dibromo *p*-hydroxycinnamoyl moiety as in **90,** but lacks the *N,N*-dimethylaminopropyl substituent on the phenolic hydroxyl group of the 3,5-dibromo *p*-hydroxycinnamoyl moiety, displayed much weaker cytotoxicity than **90**. Therefore, both *N,N*-dimethylaminopropyl and *trans*-3,5-dibromo *p*-hydroxycinnamoyl moieties seem to be essential for the cytotoxicity for this series of compounds. Moreover, **90** showed a promising in vitro acetylcholinesterase inhibitory activity with an IC_{50} of 1.3 μM, as well as a potent activity against fish antifeedant activity [34,64] (Figure 6).

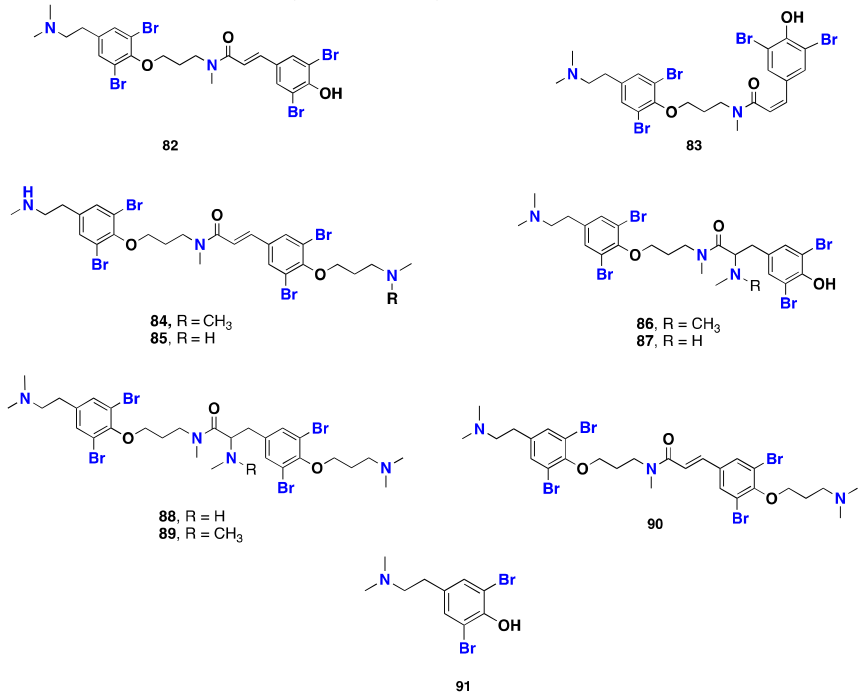

Figure 6. Chemical structures of **82–91**.

2.2. *Non-halogenated Derivatives (Tyrosine, Aaptamine, Pyrrole, Quinolines, Isopernoids, Sesterterpenoids and Macrolides)*

From Figure 7—lihouidine (**92**), a polycyclic alkaloid featuring two modified aaptamine moieties, was obtained from *Suberea* n. sp. collected in Australia. Compound **92** displayed moderate cytotoxicity against P388D1 (mouse lymphoma cells) with an IC_{50} of 3 μg/mL [65]. Interestingly, structurally less complex metabolites such as 1-(hydroxy(1*H*-pyrrol-2-yl)methyl)guanidine (**93**) and 4-(2-amino-3-methylbut-3-en-1-yl) phenol (**94**) were also isolated from the Red Sea *Suberea* sp. Compound **93** exhibited low cytotoxicity against HCT-116 and HeLa cell lines, with IC_{50} values of 25 and 30 μg/mL, respectively, whereas **94** showed moderate cytotoxicity with IC_{50} values of 20 and 27 μg/mL, respectively. Furthermore, **93** and **94**displayed moderate antifungal activity against *Candida albicans* at a concentration of 100 μg, with inhibition zones of 8 and 15 mm, respectively [50]. 5-Hydroxyxanthenuric acid (**95**) and xanthurenic acid (**96**) were co-isolated, along with **82–91,** from the Polynesian *S. ianthelliformis* [64].

A few non-brominated metabolites, including terpenoid compounds such as (+)-(5*S*,6*S*)-subersin (**97**) and three merediterpenoids including (−)-subersic acid (**98**), jaspaquinol (**99**), and (-)-jaspic acid (**100**), were also reported from *Suberea* sp. These compounds showed inhibitory activity against human 15-lipoxygenase, with IC_{50} values >100, 15, 0.3, and 1.4 μM, respectively [66]. Four sesterterpenoids, namely luffariellolide (**101**), 18-hydroxyluffariellolide (**102**), acantholides A (**103**), and C (**104**), were reported from *Suberea* sp. collected from the Philippines [67]. These naturally occurring compounds, along with synthetically prepared analogues, were evaluated for their antimicrobial activity against two Gram-negative bacterial strains, *Klebsiella pneumoniae* and *Salmonella enterica*. Compound **101** displayed moderate activity against *S. enterica* with an MIC value of 4 μg/mL, but no activity against *K. pneumoniae* (MIC value >64 μg/mL), while **102** exhibited moderate activity against *K. pneumoniae* (MIC value of 8 μg/mL) and weak activity against *S. enterica* (MIC value 16 μg/mL) [67] (Figure 7).

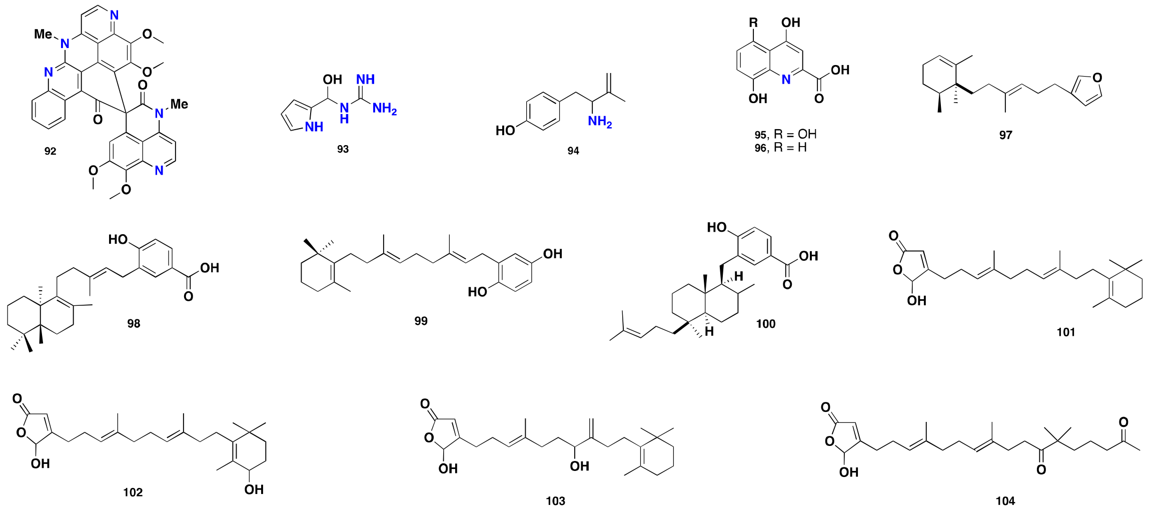

Figure 7. Chemical structures of **92–104**.

From Figure 8—additionally, three potent cytotoxic glycosylated oxazole-bearing macrolides, **105–107,** were isolated from *S. creba* collected in New Caledonia. These compounds exhibited strong cytotoxicity against seven tumor cell lines, including A549 (human lung carcinoma), BxPC3 (Human primary pancreatic adenocarcinoma), KB, KB-V1 (human cervix carcinoma), LoVo (human colon carcinoma), Namalwa (human Burkitt lymphoma), and SKOV3 ovarian carcinoma), with EC_{50} values ranging from micromolar to picomolar [68,69] (Figure 8).

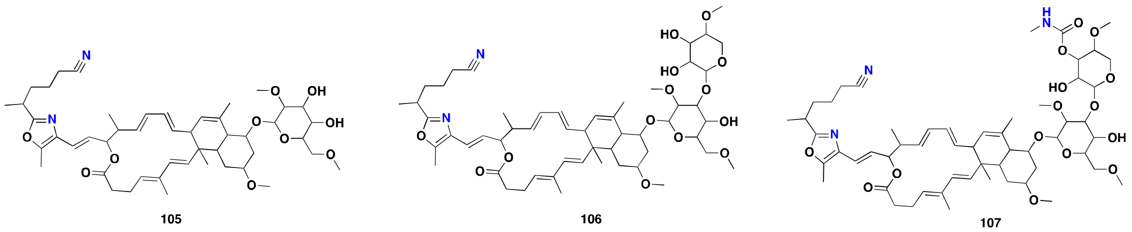

Figure 8. Chemical structures of **105–107**.

From Figure 9—curiously, only few metabolites have been reported from *Suberea* sponge-associated microorganisms. These include a dibenzopyrazine alkaloid (**108**) and five quinolone derivatives (**109–113**), along with the 2,5-diketopeiprazine alkaloid (**114)** produced by a marine bacterium *Pseudomonas* sp. isolated from *S. creba*. Compound **109** displayed promising in vitro antibacterial activity against the marine bacterium *V. scala* [46] (Figure 9).

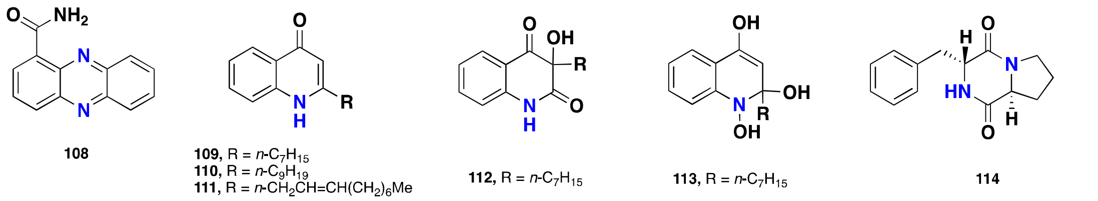

Figure 9. Chemical structures of **108–114**.

Table 1. Summary of secondary metabolites isolated from marine sponges of the genus *Suberea,* and their biological activities.

Compound	Species	Local of Collection	Biological Activity	References
1–5	*Suberea* sp.	Okinawa	Cytotoxic, kinase inhibitors	27
6–7	*Suberea* sp.	Okinawa	Cytotoxic, antibacterial	38
8–9	*Suberea* sp.	Okinawa	Cytotoxic	39
10–14	*Suberea* sp.	Guam	Nr	40
15–27	*S.* aff. *praetensa*	Thailand	Cytotoxic	41–43
24	*S. creba*	Coral Sea, Australia	Antiviral, antibacterial	45–47
28–32	*S. creba*	Coral Sea, Australia	Cytotoxic, antimicrobial	46
32–33	*S. mollis*	Red Sea, Egypt	Cytotoxic, antimicrobial	48,49
23, 30–32	*Suberea* sp.	Red Sea, Egypt	Cytotoxic, antiproliferative, antibacterial	50
34–39	*S. creba*	Coral Sea, Australia	Antimicrobial, Cytotoxic, tyrosine kinase inhibitor, antiproliferative	46, 51–53 54–58
40–41	*Suberea* sp.	Red sea, Egypt	Cytotoxic, antioxidant	30
	S. mollis	Red Sea, Egypt	Nr	59
42–44	*S. mollis*	Red Sea, Egypt	Antimicrobial	28
45–52	*S. clavata*	Great Barrier Reef, Australia	Plasma thromboplastin inhibitor	60,61
53–57	*S. ianthelliformis*	Manta Ray Bommie, Australia	Antibacterial	29
58–62	*S. ianthelliformis*	Solomon Islands	Antiplasmodial	62
63–64	*Suberea* sp.	Red Sea, Egypt	Antiproliferative	30
65–81	*Suberea* sp.	Micronesia	Cytotoxic	63
82–91	*S. ianthelliformis*	French Polynesia	Cytotoxic, acetylcholinesterase inhibitor	34,64
92	*Suberea* sp.	Lihou Reef, Australia	Cytotoxic	65
93–94	*Suberea* sp.	Red Sea, Egypt	Cytotoxic, antimicrobial	50
95–96	*S. ianthelliformis*	French Polynesia	Nr	64
97–100	*Suberea* sp.	Papua New Guinea	Human 15-Lipoxygenase inhibitor	66
101–104	*Suberea* sp.	Philippines	Antimicrobial	67
105–107	*S. creba*	New Caledonia	Cytotoxic	68–69
108–114	*S. creba*	New Caledonia	Antibacterial	46

Nr: Not reported.

3. Proposed Biogenetic Pathways for Different Bromotyrosine Derivatives

From Figure 10—earlier biosynthetic studies on bromotyrosine derivatives showed that the metabolic cascade is initiated by bromination of tyrosine (**I**) with bromoperoxidase enzymes to give a brominated tyrosine intermediate **II**. Then, **II** can be transformed into **V** (like purpurealidins A–F) or can undergo further reactions. Route **A**: Oxidation of the amine to an oxime, affording the intermediate **VI**. Route **B**: *O*-methylation of **II**, followed by the oxidation of the amine functionality to an oxime (**III**) or producing compounds such as purpuramines and aplysamines (**VIII**). Moreover, the first pathway (route **A**) could also afford phenolic nitriles (**IX**) and amides (**XII**), or alternatively, can undergo an epoxidation (**A**$_1$) to form an intermediate **VII**. This in turn leads to either (**a**) the isoxazoline ring system (**XIV**), producing metabolites such as aerothionin, homoaerothionin, purealdin Q, and purpurealidins A and J, or (**b**) the oxepine ring system (**XIII**), as found in the psammaplysins. Moreover, the isoxazoline ring (**XIV**) can undergo further oxidation and dehydration leading to **XV** (like purpurealidin B). On the other hand, route **B** could lead to the pathway featuring a dehydration/decarboxylation (**B**$_1$) to afford the *O*-methylated nitriles (**IV**) [26,70–72] (Figure 10).

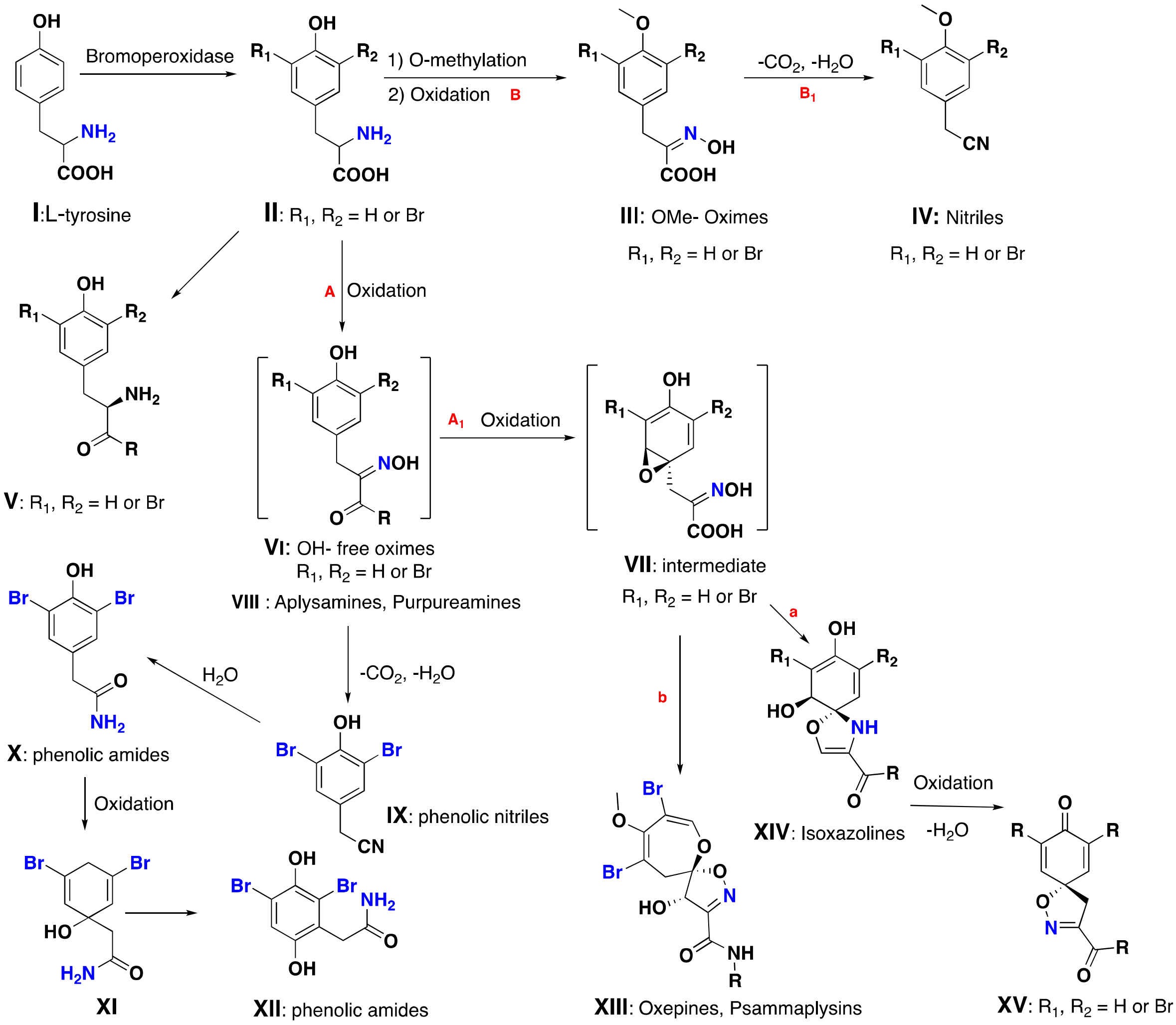

Figure 10. Proposed biogenetic pathway of different bromotyrosine derivatives.

4. Conclusions

The present review highlights a comprehensive literature survey covering the chemical and biological remarks of secondary metabolites isolated from marine sponges belonging to the genus *Suberea* over the period of 1998–2018. One hundred and fourteen isolated metabolites are categorized into two main groups, presenting an array of molecular architectures that display a vast spectrum of bioactivities. Additionally, a brief insight of the proposed biogenetic pathways leading to different bromotyrosine motifs is also discussed. The chemodiversity and bioactivities of the metabolites from the sponges of this genus make them interesting targets for further exploration to obtain novel compounds with therapeutic potentiality. Furthermore, this systematic review provides evidence that a myriad of secondary metabolites reported from members of the genus *Suberea* are structurally unique and exhibit a variety of biological/pharmacological activities, although cytotoxic activity predominated. Moreover, it can be observed that the habitats of these sponges also influence the types of compounds and consequent biological activities. These findings can be helpful in the bioprospecting process of marine sponges of this genus, and in finding new compounds as potential targets for further drug development in different therapeutic areas.

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Abbreviations

The following abbreviations are used in this manuscript:

GI_{50}	Half maximal growth inhibition
Factor XIa	Plasma thromboplastin antecedent
IC_{50}	Half maximal inhibitory concentration
MIC	Minimum Inhibitory concentration

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