Natural Products from the Marine Sponge Subgenus Reniera

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Abstract: Marine sponges are one of the prolific producers of bioactive natural products with therapeutic potential. As an important subgenus of Haliclona, Reniera sponges are mainly distributed in the Mediterranean Sea and Atlantic area, and had been chemically investigated for over four decades. By an extensive literature search, this review first makes a comprehensive summary of all natural products from Reniera sponges and their endozoic microbes, as well as biological properties. Perspectives on strengthening the chemical study of Reniera sponges for new drug-lead discovery are provided in this work.

Keywords: marine sponge; Haliclona; Reniera; endozoic microbe; natural product

1. Introduction

Marine sponges are widely distributed across oceans and represent one of the most diverse groups of primitive multicellular aquatic animals in nature. Numerous chemical investigations have indicated that this marine creature is one of the most attractive sources of precious natural products with the potential of clinical application [1]. As one of the important marine sponges found in the Mediterranean Sea and Atlantic area, Reniera was originally assigned as one genus and later classified to be one subgenus of Haliclona [2]. Morphologically, Reniera sponge has a soft texture and brownish-maroon epidermis, and its body is soft and fragile and looks like a compressed tree with simple digitate branches and spicules of various sizes [3]. Meanwhile, this marine sponge harbors a special arrangement of the flagellated chambers in the incurrent and excurrent canal systems [3]. To the best of our knowledge, the subgenus Reniera consists of at least 16 species, including R. albescens, R. coccinea, R. cratera, R. fallaciosa, R. fascigera, R. fragilis, R. fulva, R japonica, R. lacteal, R. membrana, R. mucosa, R. porosa, R. porrecta, R. reticulata, R. sarai, and R. thomasi [4].

On the basis of an extensive literature search using SciFinder and Dictionary of Natural Products databases covering up to December 2020, this review comprehensively makes an overview of all natural products from Reniera sponges and their endozoic microbes, as well as biological properties.

2. Natural Product Inventory of the Subgenus Reniera

Chemical studies of the marine sponge subgenus Reniera date back to the early 1970s. Until 2020, as many as 121 natural products had been isolated and characterized from Reniera sponges and their endozoic microbes. According to their chemical structures, these biomolecules are grouped into five types including alkaloid, terpenoid, polyketide, sterol, and cerebroside and ceramide, which are respectively introduced in detail as follows.

2.1. Alkaloids

2.1.1. 3-Alkylpyridiniums

Reniera sponge-derived 3-alkylpyridiniums are inseparable dimers or polymers with various degrees of polymerization (DP) and different lengths of alkyl chains. Usually,
polymeric 3-alkylpyridinium salt (Poly-APS) possesses a broad spectrum of biological properties, including a potent inhibitory effect on acetylcholinesterase and phosphatase 2A, and cytotoxic, hemoclasia, and proarrhythmogenic activity [5–13]. Moreover, these natural products had been found to inhibit microfouling, and the proliferation and movement of susceptible algae and biofilm bacteria [14–16]. The chemical study of Reniera sp. collected from Pemba Island (Tanzania) afforded three novel cyclic 3-alkylpyridiniums named njaoaminiums A (1), B (2), and C (3) (Figure 1), of which compound 2 has weak cytotoxicity against three human tumor cell lines A549 (lung carcinoma), HT29 (colon carcinoma), and MDA-MB-231 (breast) with Gl50 values of 4.1, 4.2, and 4.8 µM, respectively [17]. Two cyclic poly-APSs (4 and 5) with a respective DP of 29 and 99 were separated and characterized from the Mediterranean specimen of R. sarai [18]. One search for the chemical synthesis of poly-APS resulted in the production of three novel analogs APS8 (6), APS12-2 (7), and APS3 (8), of which compound 8 is a mixture of two polymers with DPs of 10 and 32 covalently linked N-butyl-3-butyl pyridinium units in a 9:1 ratio. Bioassay suggested that compound 6 exhibited a toxic effect on the non-small cell lung cancer (NSCLC) tumor cell line but nontoxicity against normal lung fibroblasts [9], while 7 could cause vascular smooth muscle contraction and a decrease in arterial blood pressure and 8 could block muscle-type nicotinic acetylcholine receptors (nAChRs) [19,20].

![Figure 1. 3-Alkylpyridiniums 1–5 from the subgenus Reniera and their derivatives 6–8.](image)

### 2.1. Quinolones and Isoquinolines

Bioassay fractionation of the 2-propanol crude extract of Reniera sp. collected from the Njao area (Tanzania) afforded eight new polycyclic quinolines and njaoamines A–G and I (9–16) (Figure 2); compounds 9–14 demonstrated potent cytotoxicity against human tumor cell lines colon H-T29, lung A-549, and breast MDA-MB-231 with Gl50 values ranging from 1.5 to 7.2 µM; and compound 16 had cytotoxic effect on three human tumor cell lines including MDA-MB-231 (breast), HT-29 (colon), and NSLC A-549 in the micromolar range [21,22]. Chemical analysis of the similar specimen collected in Isla Grande (Mexico) afforded nine antimicrobial isoquinolines (17–25), including five monomers renierone (17), 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (18), N-formyl-1,2-dihydrorenierone (19), O-demethylrenierone (20), and mimosamycin (21), and four dimers renieramycins A–D (22–25) [23,24]. In addition, two new polycyclic isoquinoline dimers, renieramycins E (26) and F (27), were purified from another Reniera specimen collected from Palau [25].

### 2.1.3. Macrocyclic Diamines

To the best of our knowledge, all macrocyclic diamine-producing Reniera sponges were collected from the Mediterranean. Saraines A–C (28–30) (Figure 3) were obtained from the Mediterranean sponge R. sarai and exhibited a broad spectrum of biological activities, including insecticidal and acaricidal potency to the arthropoda Macrosiphum euphorbiae (Thos.), Tetranychus urticae Koch, and Aedes aegypti L.; strong inhibitory effect on Streptococcus agalactiae and AChE; and high hemolysis [26–28]. Chemical synthesis of compound 28...
had first been achieved by Garg and coworkers in 2006 [29]. Isosaraine-1–3 (31–33) were three new hexahydro-quinolizin-2(6H)-one derivatives and their absolute stereochemistry was unambiguously determined using the modified Mosher’s method [30–32]. One novel macrocyclic alkaloid, misenine (34), was purified from unclassified Reniera sponge collected in the Bay of Naples (Italy) [33]. Unfortunately, no report of their bioactivity has been published until now.

Figure 2. Quinolines and isoquinolines 9–27 from the subgenus Reniera.

2.1.4. Other Alkaloids

A search for antimicrobial substance(s) from an unidentified Reniera sponge from Isla Grande (Mexico) led to the isolation of one new isoindole-4,7-dione derivative (35) (Figure 4) [24], which was chemically synthesized through the cycloaddition of a non-stabilized azomethine ylide and a quinone by Parker and coworkers in 1984 [34]. Chro-

Figure 3. Macrocyclic diamines derivatives 28–34 from the subgenus Reniera.
matography on a column of a cation exchange resin of the n-butanol soluble fraction from the acetone extracts of the sponge *R. cratera* afforded one simple nitrogenous compound 2-aminimidazole (36) [35]. One cyclic depsipeptide renieramide (37) was also isolated and characterized from *Reniera* sp. No. 2115 collected on the Island of Santo (Vanuatu) [2]. Bioassay-guided fractionation of the MeOH extract of one marine sponge *Haliclona (Reniera)* sp. collected off Ulleung Island (Korea) led to the discovery of a new sphingosine (38) together with two lysophosphatidylcholines (39 and 40), which exhibited moderate cytotoxicity against a panel of five human solid tumor cell lines including A549, SK-OV-3, SK-MEL-2, XF498, and HCT15 [36].

![Figure 4](image4.png)

**Figure 4.** Other alkaloids derivatives 35–40 from the subgenus *Reniera*.

### 2.2. Terpenoids

Structurally, most of terpenoids produced by *Reniera* sponges are tetraterpenes except the sesquiterpenoid fulvanin 1 (41) (Figure 5) [37]. Interestingly, these tetraterpenes are carotenoid analogs, including acetylenic carotenoids (42–43), renieratene (44), isorenieratene (45), and renierapurpurin (46) from *R. japonica* [38,39]. It is noteworthy that two symbiotic strains, *Flexibacter* sps. DK30213 and DK30223, isolated from *R. japonica*, were found to produce zeaxanthin (47), which is one of the commonly used antioxidant agents [40]. Two new cytotoxic meroditerpenes, halioxepine B (48) and halioxepine C (49), along with halioxepine (50), were isolated from two Indonesian sponges of the genus *Haliclona (Reniera)* and structurally determined by QM/NMR-DFT (quantum mechanics combined with nuclear magnetic resonance parameters calculated by density functional theory approximations) analysis [41]. It is noteworthy that compound 50 had first been synthesized and the absolute configuration at position C15 was revised as S [42].

![Figure 5](image5.png)

**Figure 5.** Terpenoids 41–50 from the subgenus *Reniera*. 
2.3. Polyketides

2.3.1. Aromatic Polyketides

Polyketides are one of the major groups of Reniera-derived secondary metabolites, such as aromatic and aliphatic polyketides. As many as eighteen aromatic polyketides (51–67) (Figure 6) had been separated from R. fulva and R. mucosa, which were respectively collected from the Egadi Islands (Italy) and Tarifa Island (Spain) [37,43]. Compounds 52, 53, 56, and 59 possessed in vitro cytotoxicity against P388 mouse lymphoma, A549 human lung carcinoma, HT29 human colon carcinoma, and MEL28 human melanoma cell lines with the same ED₅₀ values of 5 µg/mL [43]. Moreover, compound 59 exhibited a moderate inhibitory effect on DHFR (dihydrofolate reductase) with an ED₅₀ value of 3 µg/mL. At the concentrations from 10⁻⁴ to 10⁻⁶ M, compounds 61 and 63 were shown to be cytotoxic to the NCI-H522 nonsmall lung cancer cell line and CCRF-CEM leukemia cell line, while 54 had more selective cytotoxicity against the latter [37].

Figure 6. Aromatic polyketides derivatives 51–67 from the subgenus Reniera.

2.3.2. Aliphatic Polyketides

Linear alkynols and alkynones are the most common aliphatic polyketides detected in the marine sponge R. fulva. Fulvinol (68, Figure 7), a new long-chain diacetylenic compound, was purified from R. fulva collected at Algeciras Bay (Spain) and found to possess an inhibitory effect on P-388 mouse lymphoma, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 human melanoma cell lines with the same ED₅₀ values of 1 µg/mL [44]. One search for secondary metabolites of R. fulva from the Mediterranean Sea resulted in the isolation of five new acetylenic compounds including debrorenierin-1 (69), renierin-1 (70), lb-dihydrorenierin-1 (71), renierin-2 (72), and 18-hydroxyrenierin-2 (73) [45].

Figure 7. Aliphatic polyketides 68–73 from the subgenus Reniera.
2.3.2. Aliphatic Polyketides

Linear alkynols and alkynones are the major polyketide metabolites from the sponge Haliclona (Reniera) sp. J01U-6 from Ulleung Island (Korea) [36].

2.3.3. Other Polyketide

One new bicyclic eicosanoid named mucosin (74) (Figure 8) was detected in the acetone extracts of R. mucosa samples, which had been collected in different areas including Blanes (Spain), Grotte de Jarr (France), Massalubrense, and Procida (Italy) [46]. Interestingly, this metabolite contains an unusual bicyclo [4.3.0] nonane skeleton with equilibrium of normal physiology in mammalian systems.

![Figure 8. Other polyketide 74 from the subgenus Reniera.](image)

2.4. Sterols

To date, a total of 27 sterol derivatives (75–101) (Figure 9) have been obtained and characterized from Reniera sponges. Chemical analysis of one unidentified sample (#063176) deposited at California Academy of Sciences Museum afforded eleven sterols (74–85) [47], and another specimen (R. sarai) collected from the Bay of Naples (Italy) resulted in the isolation of ten sterols (87–96) [48]. Using vacuum liquid chromatography (VLC), flash column chromatography, and preparative thin-layer chromatography (PTLC), β-sitosterol (97) was purified from ethyl acetate extract of Halicloina (Reneira) fascigera sponge (SPV06/12/13) collected off Samalona Island (Indonesia) [49]. Along with three alkaloids (38–40), six sterol analogs 77, 86, and 98–101 were separated from the MeOH extract of the sponge Halicloina (Reneira) sp. J01U-6 from Ulleung Island (Korea) [36].

![Figure 9. Sterols 75–101 from the subgenus Reniera.](image)

2.5. Cerebrosides and Ceramide

Cerebrosides are a group of glycosphingolipids consisting of a glucose or galactose residue attached to a ceramide moiety containing one sphingoid base and an amide-linked
long fatty acyl chain. These amphipathic biomolecules are important components of tissues and organs in organisms and possess a broad spectrum of biological functions such as antifungal, antitumor, antiviral, an inhibitory effect on histidine decarboxylase, and cytotoxicity [50]. Chemical analysis of the n-hexane layer of the MeOH extract of the same specimen Haliclonia (Reniera) sp. J01U-6 collected off the coast of Ulleung Island (Korea) afforded twenty-one new cerebrosides (101–111, 113–122) together with one known analog (112), which possess unprecedented unsaturated or saturated long (C_{15}–C_{29}) alkyl chains (Figure 10) [51,52]. This was the first report on the isolation of isomeric pairs of glucocerebrosides containing saturated C_{15} and C_{19} acyl chains. Lately, the structural determination of compounds 109–112, 115, 116, 120, and 121 were well established using fast atom bombardment mass spectrometry (FAB-MS) in positive-ion mode by Hong and coworkers [53]. In addition, one ceramide (123) was separated from the same sponge SPV06/12/13 collected off Samalona Island, and its absolute structure was determined by HyperChem computational techniques [49].

![Cerebrosides 102–123 and ceramide 124 from the subgenus Reniera.](image-url)

### 3. Conclusions and Perspectives

The marine sponge subgenus Reniera is one of the most prolific sources of natural products possessing various chemical structures and biological properties, such as cytotoxic poly-APS derivatives, insecticidal and acaricidal sarains A–C (28–30), and antioxidant zeaxanthin (47). In the recent decade, however, few reports on biological and chemical studies of Reniera sponge had been published. In comparison with those of other marine sponge genera such as Agelas [54] and Phyllospongia [55], chemical investigations of Reniera sponges seem to be less intensive. Therefore, great efforts should be made to carry out global resource surveys and collections of Reniera sponges and chemical studies using hyphenated technology, such as GC-MS and LC-MS-NMR. Furthermore, more attention should be paid on genome mining and the chemical study of symbiotic microorganisms of Reniera sponges as these microbes are potential producers of bioactive secondary metabolites originally derived from their hosts [56–58].

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27. Bernard, D. The Saraine Alkaloids. Alkaloids Chem. Biol. 2014, 73, 223–329.
28. Defant, A.; Mancini, I.; Raspor, L.; Guella, G.; Turk, T.; Sepic, K. New structural insights into saraines A, B, and C, macrocyclic alkaloids from the marine sponges Reniera (Haliclona) sarai. Eur. J. Org. Chem. 2011, 3761–3767. [CrossRef]
29. Garg, N.K.; Becker, M.H.; Chua, P.; Downham, R.; Douglas, C.J.; Hiebert, S.; Jaroch, S.; Matsuoka, R.T.; Middleton, J.A.; Ng, F.W.; et al. Total Synthesis of (−)-Sarain A. In Proceedings of the 23rd ACS National Meeting, San Francisco, CA, USA, 10–14 September 2006; American Chemical Society: Washington, DC, USA, 2006; p. ORGN-857.
30. Cimino, G.; Spinella, A.; Trivellone, E. Isosarain-1. A new alkaloid from the Mediterranean sponge Reniera sarai. Tetrahedron Lett. 1989, 30, 133–136. [CrossRef]
31. Guo, Y.; Madaio, A.; Scognamiglio, G.; Cimino, G. Further studies of alkaloids from Reniera sarai: Structures of saraine-3 and isosaraine-3; absolute stereochemistry of saraine-1 and saraine-2. Tetrahedron 1996, 52, 14961–14974. [CrossRef]
32. Cimino, G.; Fontana, A.; Madaio, A.; Scognamiglio, G.; Trivellone, E. Application of two-dimensional shift correlated NMR techniques to the structure determination of an unusual marine alkaloid, isosaraine-2. Magn. Reson. Chem. 1991, 29, 327–332. [CrossRef]
33. Guo, Y.; Trivellone, E.; Scognamiglio, G.; Cimino, G. Misenenine, a novel macrocyclic alkaloid with an unusual skeleton from the Mediterranean sponge Reniera sp. Tetrahedron 1998, 54, 541–550. [CrossRef]
34. Parker, K.A.; Cohen, I.D.; Padwa, A.; Dent, W. Cycloadditions of non-stabilized azomethine ylides and quinones. Synthesis of the Reniera isoidole. Tetrahedron Lett. 1984, 25, 4917–4920. [CrossRef]
35. Cimino, G.; De Stefano, S.; Minale, L. Occurrence of hydroxyhydroquinone and 2-aminoimidazole in sponges. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 1974, 47, 895–897. [CrossRef]
36. Mansoor, T.A.; Park, T.; Luo, X.; Hong, J.; Lee, C.O.; Jung, J.H. A new sphingosine from a marine sponge Haliclona (Reniera) sp. Nat. Prod. Sci. 2007, 13, 247–250.
37. Casapullo, A.; Minale, L.; Zollo, F. Paniceins and related sesquiterpenoids from the Mediterranean sponge Reniera fulva. J. Nat. Prod. 1993, 56, 527–533. [CrossRef] [PubMed]
38. Hamasaki, T.; Okukado, N.; Yamaguchi, M. Two natural acetylenic aromatic carotenoids. Bull. Chem. Soc. Jpn. 1973, 46, 1884–1885. [CrossRef]
39. Yamaguchi, M. Total syntheses of renieratene and renierapurpurin. Bull. Chem. Soc. Jpn. 1960, 33, 1560–1562. [CrossRef]
40. Miki, W.; Otaki, N.; Yokoyama, A.; Kusumi, T. Possible origin of zeaxanthin in the marine sponge, Reniera japonica. Experientia 1996, 52, 93–96. [CrossRef]
41. Tarazona, G.; Benedit, G.; Fernandez, R.; Perez, M.; Rodriguez, J.; Jimenez, C.; Cuevas, C. Can stereocenters separated by two methylene groups be related by DFT Studies? The case of the cytotoxic meroditerpenes halioxepines. J. Nat. Prod. 2018, 81, 343–348. [CrossRef]
42. Poock, C.; Kalesse, M. Total synthesis and structure revision of halioxepine. Chem. Eur. J. 2021, 27, 1615–1619. [CrossRef]
43. Zubia, E.; Ortega, M.J.; Carballo, J.L.; Salva, J. Sesquiterpene hydroquinones from the sponge Reniera mucosa. Tetrahedron 1994, 50, 8153–8160. [CrossRef] [PubMed]
44. Ortega, M.J.; Zubia, E.; Carballo, J.L.; Salva, J. Fulvinol, a new long-chain diacetylenic metabolite from the sponge Reniera fulva. J. Nat. Prod. 1996, 59, 1069–1071. [CrossRef]
45. Cimino, G.; De Stefano, S. New acetylenic compounds from the sponge Reniera fulva. Tetrahedron Lett. 1977, 18, 1325–1328. [CrossRef]
46. Casapullo, A.; Scognamiglio, G.; Cimino, G. Mucosin: A new bicyclic eicosanoid from the Mediterranean sponge Reniera mucosa. Tetrahedron Lett. 1997, 38, 3643–3646. [CrossRef]
47. Lawson, M.P.; Stoilov, I.L.; Thompson, J.E.; Djerrassi, C. Cell membrane localization of sterols with conventional and unusual side chains in two marine demosponges. Lipids 1988, 23, 750–754. [CrossRef]
48. Dini, A.; Piccilli, V.; Pronzato, R.; Sica, D. Sterol composition of marine sponges Stryphnum muncratus and Reniera sarai. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 1985, 81B, 111–114. [CrossRef]
49. Sapar, A.; Ahmad, A.; Soekamto, N.H.; Noor, A. Isolation and characterization of a ceramide and β-sitosterol compounds on Haliclona (Reniera) fascigera from Spermonde Archipelago. Int. J. ChemTech Res. 2017, 10, 52–61.
50. Tan, R.X.; Chen, J.H. The cerebrosides. Nat. Prod. Rep. 2003, 20, 509–534. [CrossRef]
51. Mansoor, T.A.; Shinde, P.B.; Luo, X.; Hong, J.; Lee, C.O.; Sim, C.J.; Son, B.W.; Jung, J.H. Renierosides, cerebrosides from a marine sponge Haliclona (Reniera) sp. J. Nat. Prod. 2007, 70, 1481–1486. [CrossRef] [PubMed]
52. Park, T.; Mansoor, T.A.; Shinde, P.B.; Bao, B.; Hong, J.; Jung, J.H. New cerebrosides from a marine sponge Haliclona (Reniera) sp. Chem. Pharm. Bull. 2009, 57, 106–111. [CrossRef] [PubMed]
53. Ahn, Y.M.; Lee, W.W.; Jung, J.H.; Lee, S.G.; Hong, J. Structural determination of glucosylerceramides isolated from marine sponge by fast atom bombardment collision-induced dissociation linked scan at constant B/E. J. Mass. Spectrum. 2009, 44, 1698–1708. [CrossRef] [PubMed]
54. Zhu, J.Y.; Liu, Y.; Liu, Z.J.; Wang, H.; Zhang, H.W. Bioactive nitrogenous secondary metabolites from the marine sponge genus Haliclona. Mar. Drugs 2019, 17, 682. [CrossRef] [PubMed]
55. Zhang, H.W.; Dong, M.L.; Wang, H.; Crews, P. Secondary metabolites from the marine sponge genus Phyllospongia. Mar. Drugs 2017, 15, 12. [CrossRef] [PubMed]
56. Zhang, H.W.; Zhao, Z.P.; Wang, H. Cytotoxic natural products from marine sponge-derived microorganisms. *Mar. Drugs* **2017**, *15*, 68. [CrossRef] [PubMed]

57. Asagabaldan, M.A.; Ayuningrum, D.; Kristiana, R.; Sabdono, A.; Radjas, O.K.; Trianto, A. Identification and antibacterial activity of bacteria isolated from marine sponge *Haliclona (Reniera)* sp. against multi-drug resistant human pathogen. In *IOP Conference Series-Earth and Environmental Science, Proceedings of 2nd International Conference on Tropical and Coastal Region Eco Development 2016, Diponegoro University, Bali, Indonesia, 25–27 October 2016*; IOP Publishing: Bristol, UK, 2017.

58. Bai, X.; Dong, M.; Lai, T.; Zhang, H. Antimicrobial evaluation of the crude extract of symbiotic fungi from marine sponge *Reniera japonica*. *Bangladesh J. Pharmacol*. **2018**, *13*, 53–56. [CrossRef]