A Review on Diversity of Anticancer Compounds Derived from Indonesian Marine Sponges

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Abstract. As a tropical archipelago country, Indonesia has a mega diversity of marine organisms, such as sponges. About 850 species of sponges were identified from the east part of Indonesia. The uniqueness of Indonesian marine sponges attracted many researchers to explore the sponge’s potential in producing active substances. During 1995-2016, about 40 genera of Indonesian sponges were investigated for their potential in producing pharmacological activity such as antimicrobial, anticancer, antiviral, multidrug-resistant (MDR), etc. The data showed that 56.7% of 430 reported compounds were confirmed as new compounds. The research trend on Indonesian sponges was high during 2004-2013, but decreasing after 2014. However, researches in the term of active substances from marine sponges should find provide the basic skeleton of anti-cancer drug lead compounds. Chemical structure diversity plays an important role in the exploration of anticancer lead compounds. The purpose of this paper is to review the potential of anticancer diversity compounds derived from Indonesian sponges, to get comprehensive data for further investigation. As the conclusion of our review, the most anticancer compounds derived from Indonesian marine invertebrates are alkaloid groups (such as aaptamine, manzamine, and bromopyrrole derivatives), then terpenoid groups (such as diterpene, coelodiol, and coeloic acid, sesquiterpene aminoquinone, and also (+)-curcuphenol and (+)-curcudiol), and also from the other groups such as sterole, peptide, polyketide, amino acid derivatives, natural organic acid, and quinone. The most effective anticancer compounds were 5-benzoyldemethylaaptamine, isoaaptamine, 3-bromofascaplysin, hyrtioreticulins A, stylissamide X, sigmosceptrellin B, and diacarperoxide S.

Keywords: diversity, active compounds, anti-cancer, sponges, marine resources

1. Introductions
Cancer is the third highest cause of mortality in Indonesia after heart disease and stroke [44]. Cancer death cases in Indonesia increased from 1.3-1.8% during 2013-2018 [1]. According to the data from the Indonesian Ministry of Health, the number of death cases caused by cancer in 2018 was 207,221 cases in Indonesia and 9.6 million cases worldwide. The costs incurred for handling cancer reached 3.41 trillion rupiahs/year. Indonesian government implemented several programs such as the socialization of healthy living, cancer early detection, improvement of health facilities, and availability of cancer drugs. Currently, the availability of imported drugs for cancer treatment is limited and expensive. Consequently, the drugs are not affordable for cancer patients from middle to lower class society. The development of cancer drugs, either herbal medicine or modern medicine for chemotherapy, aimed to solve this crucial issue. The investigation to develop cancer drugs in
Indonesia mostly focused on the terrestrial plant with a small part that focused on marine organisms. Nonetheless, marine organisms have been recognized as the producer of active compounds with high potential, especially for anticancer.

The collected publications during 1985 to 2012, were reported there were 16,617 new compounds derived from marine organisms. Almost 30% of the reported compounds were derived from the marine sponges [4]. A total of 4196 or 25.25% of the reported compounds were pharmacologically active and 56% of them were confirmed as anticancer [2]. The review about the potency of marine biotas as a source of potential active natural products was done by hanif et al [7]. Ye et al also reported that marine sponges were the vital source of anticancer diversity such as sterol, terpene, alkaloid, peptide, macrolide, polyketone, etc [45].

The purpose of this study was to find the potential anticancer compounds by reviewing the previous study concerning to the diversity of chemicals derived from Indonesian sponges. Studies on the chemical diversity of potential anticancer substances are needed to find the potential lead compounds. By increasing the chemical diversity, the chance to obtain the potential lead compound candidate becomes bigger. Screening of the chemical structures using the cheminformatics approach will be more effective by cutting several steps in the drug discovery strategy. "This study is one of the interesting issues to be discussed to find a new strategy in anticancer drug discovery. The one approach was by the compilation of other studies and previous findings in this paper

2. Indonesian sponge as the bioactive compounds reservoir.

Sponge-derived bioactive compounds became interesting issue to be explore since the finding of several potential drug candidates. The spongouridine group with more than 300 analog compounds was part of the results of antitumor drug exploration [4]. The study on Indonesian sponge biodiversity was firstly conducted in 1889 through Sibolga expedition, but most of the specimen was unpublished. The second expedition was Snellius II (1987) that reported 830 species of sponge identified from eastern Indonesia in combination with the specimen from the previous expedition. Most of them were H. massa, Druinella p., Haliclona violacea, Acanthella c., H. fascigera, C. schulzei, Spirastrella decumbens, Cliona spec. and Ircinia irregu. [6].

The investigation of Indonesian Sponge’s natural products were started in early 1970. During 1970-2017, A total number of 498 novel molecules were reported produce by Indonesian sponges [7]. The reported sponges-derived natural products were mostly produced by three classes: Demospongiae (91.8%), Homoscleromorpha (6.6%), and Calcarea (1.6%). The highest genera reported were Achantostrongylophora (4.4%), Xestospongia (3.6%), Sinularia (3.4%), Apysinella, Theonella and Strepsichordaia (2.9% each), Plakortis, Petrosia, Spongia, Melophlus (2.6% each), Agelas, Rhabdasterella, and Lissoclinum (2.5% each) [7]. The profile of the Indonesia sponge could be seen in figure 1

![Figure 1. The profile of Indonesian sponge (Callyspongia sp, Theonella sp, pinky sponge, red rope sponge)](image)

Sponges specimen were collected using scuba diving on the 5-10 m depth. The specimen was split for identification purposes and chemical separation. During transportation from the sampling location the sponge were keep fresh by using dry ice. After arriving to the laboratory fresh sample then transfer to
the -20°C freezer. The sponges' specimen was identified by the taxonomist and the extraction until profiling the active compounds was done for producing the publication. The review of the Indonesian sponge publications during 1995-2016, get the data that among 244 papers, 430 reported compounds were derived from sponges, 244 of them confirmed as a novel metabolite. Most of the isolated compounds were active anticancer with various cell lines and mechanisms. The Indonesian sponge's natural products publications were started in 1995, became increasing since 2000 until 2013. Start from 2014 right now become decreasing, it’s caused by changing trends of investigation from unculturable to culturable sources like bacteria. Thus, the investigation of new anticancer drug compounds derived from sponge's associated bacteria is still in progress.

### 3. Diversity of anticancer compounds derived from Indonesian Sponge.

The diversity of anticancer compounds derived from Indonesian sponges will be discussed in this paper as the result of our review to the previous publication which focus on the chemical class of steroid, terpenoid, alkaloid, peptide, and the mixture basic skeleton groups.

#### 3.1 Steroid & Terpenoid

A-nor sterol with rare D-ring unsaturated, 3- (hydroxymethyl)-A-nor-5-cholest-14-en-16-one was reported derived from sponge *Axinella carteri* Dendy, 1889 (Demospongiae: Halichondrida: Axinellidae), that collected in Derawan Island, Indonesia. The bioactivity of a fraction where this compound was isolated showing moderate inhibiting tumor cell lines (P 388, A 549, and HT 29) with IC$_{50}^{}$ about 5 mg mL$^{-1}$ [8]. Another sterol reported produced by Indonesian sponge *Dasychalina* sp. was haplosamate A, the sterol containing a sulfate and a methyl phosphate group, along with its new desulfo analog. The evaluation by observing the interaction of CB1 and CB2 receptors of these analogs compounds was done using binding test. The binding test showed that desulfohaplosamate was low selectivity to the CB2 receptors, and the semi-synthetic derivative with cleaved ring B showed a completely loss of affinity for both receptors [9].

The isocopalane diterpenes coelodiol and coelolic acid were the oxidative degradation activity which in the *Coelocarteria cf. singaporesensis*. Both compounds were reported active against MKN-45 cell line (with IC$_{50}^{}$ 20 and 40 µg/mL respectively) [10]. The 20,24-bishomo-25-norscalaranes and 20,24-bishomoscalaranes have been yielded by the Indonesian marine sponge *Carteriospongia foliascens*. Those compounds were active inhibiting RCE-protease activity [11]. Meroditerpene halioxepine was yielded from *Haliclona* sp collected from Indonesia. This compound showed moderate activity against NBT-T2 cells line with IC$_{50}^{}$ 4.8 mg/ml [12]. The strongylophorine, a meroditerpene compound was found in the *Petrosia corticata* and active as proteasome inhibitors. The hemiacetal strongylophorines-13/-14 was demonstrated as the strongest proteasome inhibitor with an IC$_{50}^{}$ 2.1 µM [13].

The study of bioactive compounds derived from *Abynissia* sp yielded two sesquiterpenoid bisabolene type, (+)-curcuphenol and (+)-curcudiol. The (+)-curcuphenol was confirmed active inhibiting protein kinase SRC with IC$_{50}^{}$ 7.8 µg/mL, while (+)-curcudiol was active inhibiting FAK with IC$_{50}^{}$ 9.2 µg/mL [14]. The other reported sesquiterpene, 5-epi-smenospongione, and nine quinone phenols were reported derived from the Indonesian sponge *Dactylospongia elegans*. Among ten evaluated compounds, six of them were showed activity for inducing K562 cells line. The structure-activity relationship study demonstrated that the amino group play a role in-inducing K562 cells [15]. Furospinosulin-1, isolated from Indonesia sponge showed selectivity antiproliferative against DU145 human prostate cancer cells line at concentration 1 to 100 µM. The in vivo test of furospinosulin-1 confirmed that this compound active against S180 cells line at 10–50 mg/kg BW [16]. Two unique sesterterpenes, hyattellactones A and B, also reported produced by sponge *Hyattella* sp. Hyattellactone A was reported inhibiting PTP1B activity with IC$_{50}^{}$ as 7.45 µM, while hyattellactone B showed much less activity [17].
Chemical separation of active compounds derived from *Diacarnus megaspororhabdosa* yielded norterpene derivatives such as, diacarperoxides D to G, and diacardiol A. Those compounds were active against L.5178Y, HeLa and PC12 cell lines with EC$_{50}$ values 0.06-4.8; 0.6-10; and 0.8-10 µg/mL respectively [18].

3.2. Alkaloid

The first alkaloid group with reported having anticancer activity produced from Indonesian sponges is aaptamine or benzonaphthyridine. This compound was decided as chemotaxon of Aaptos genus especially found in *Aaptos suberitoides*. The investigation of this species collected from Carita bay West Java found aaptamine that active against human osteosarcoma (MG63Huc+) [19]. Still in the same species but different sampling location from Ambon coastal area generated aaptamine, demethyl aaptamine, and 5-benzoyldemethylaaptamine. These compounds inhibited the growth of L5178Y cells line with IC$_{50}$ 8.3;0.9; and 5.5 µM, respectively [20] also HeLa cells [21]. Isoaaptamine isolated from Indonesian *Aaptos* sp. strongly inhibited murine leukemia cell line P338 with IC$_{50}$ 0.28 µg/mL. Modification in C9 from this isoaaptamine generated compounds that showed strong activity against leukemia cell line K-5629. Those compounds were 9-O-4-trifluoromethoxybenzoylisoaaptamine and 9-O-4-tert butylbenzoylisoaaptamine, 9-O-4-pentylbenzoylisoaaptamine with GI$_{50}$ values are 1.66 ,0.05 and 1.9 µM, respectively.[22].

The second sponge derived alkaloid group is manzamine. Manzamine is β-carboline pentacyclic alkaloid that reported potential pharmacological activities, including anticancer activity [23]. Recently there are about 100 of manzamines analogs were reported produce by marine sponge with the sampling location along the Red Sea until the Indonesian [24]. The first manzamine from Indonesian sponges was reported by Ohtani research group [25]. The another manzamine group, kauluamine isolated from *Prianos* sp., reported having immunosuppressive activity. Other related compounds were pre-neo-kauluamine, neo-kauluamine, and manzamine A isolated from *Acanthostrongylaphora ingens* that was active asas proteasome inhibitor activity [26]. Manzamine A derived from Manado *Acanthostrongylaphora* demonstrate inhibiting cervical cancer cell C33A and HeLa with IC$_{50}$ 2.1 and 4 µM, respectively [27]. Manzamine A also reported remarkable activity against cervical cancer (C33A, HeLa, SiHa, and CaSki) with very low and non-cytotoxic (IC50 up to 4 µM) [46].

Investigation of potential active compounds from *Agelas linnaei* and *Agelas nakamura* generated 24 alkaloid group that illustrating bromopyrrole and another diterpene alkaloids. *A. linnaei* was reported generating 16 bromopyrrole groups., Agelanesins A–D with the unique iodinated tyramine revealing cytotoxic against L5178Y cells line with IC$_{50}$ from 9.25 to 16.76 µM. Another study to *A. nakamura* exhibiting eight alkaloids including agelatine D and its oxime derivative, also longamide C. Agelatine D and its derivatives showing cytotoxic against L5178Y with IC$_{50}$ 4.03 and 12.5 µM [28]. Another brominated alkaloid was bromotyrosine group, the resulted work of Aplysinellidae generated seven bromotyrosine derivatives, purpuramine M–N (1–2) and araplysillin VII–XI (3–7). The pharmacological activity evaluation of purpuramine M was reported that this compound inhibiting A2780S, A2780SCP5, and U251MG cancer cell lines with IC$_{50}$ values 20 µM, 40 µM, and 50 µM, respectively. In additional the guanidino moiety course decreasing the activity against these cell line[29].

Three new compounds 3-bromofascaplysin, 14-bromoreticulatine, and 14-bromoreticulate were reported produce by *Fascaplysinopsis reticulata* that collected from Pahena in the Pulau-Pulau Region Indonesia. These compounds were screened for several cell lines, and the most potential anticancer was 3-bromofascaplysin against melanoma cell line (MALME-3M) with IC$_{50}$ value 0.45 µM. The activity of this compound against several colon, melanoma, ovarian, renal, and breast cancer cell lines showed moderate until strong activity with an IC$_{50}$ in the range of 0.45-4.4 µM [30].

The pentacyclic alkaloids, papuamine and haliclonadiamine, that isolated from Indonesian sponge *Haliclona* sp inhibited cell proliferation of six human cancer cell lines with IC$_{50}$ values of 0.93–1.50 and 1.00–4.44 mM, respectively [31].
The other sponge’s alkaloid hyrtioreticulins A and B were potential inhibited ubiquitin-activating enzyme (E1) with $IC_{50}$ values of 0.75 and 11 µg/mL, respectively. Both of those compounds were isolated from the Indonesian *Hyrtios reticulatus* [32]. The Indonesian sponge *Leucetia chagosensis* contained naamine group. naamineA and naamine G showed a weak cytotoxic against mouse lymphoma (L5178Y) and human cervix carcinoma (HeLa) cell lines [33]. In contrast, naamidines H and I were presented the strong cytotoxic against HeLa cells ( $IC_{50}$ 5.6 and 15 )[34].

3.3. Peptide

Chemical investigation of *Siliquariaspongia mirabilis* reported the cytotoxic theopapuamides A-C that active against human colon carcinoma (HCT-116) cells with $IC_{50}$ values from 2.1to 4.0 µg/m [35]. The peptide spongiacidin C was generated from the *Stylissa massa* that showed inhibiting USP7. with an $IC_{50}$ of 3.8 µM [36]. A very potential HeLa cell inhibitor stylissamide X was reported produce by *Stylissa* sp. sponge. The IC50 of sstyllissamide X against HeLa cells migration was in the ranges of 0.1–10 µM [37].

The study of Indonesian *Theonella swinhoei* was reported two tridecadepsipeptides theonellapeptolide and sulfanyltheonellapeptolide. Both of these compounds demonstrated moderate antiproliferative activity against HepG2, a hepatic carcinoma cell line with an $IC_{50}$ of 1.5µM [38].

The chlorinated peptides, sintokamides A - E were isolated from the Indonesian *Dysidea* sp. Sintokamide A active inhibited prostate cancer cells [39].

3.4. Others

The polybrominated diphenyl ether compound derived from sponge Indonesian *Lamellodysidea herbacea* showing active moderate cytotoxic against two human cancer cell lines, HCT-15 (colon) and Jurkat (T-cell lymphoma) cells with $IC_{50}$ values 12 and 9.5 μM respectively [31].

The extraction of lipid contained in *Lendenfeldia* sp. Sponge yielded furanalipid, and three homoscalarane sesterterpenes . This naphthalene dimer and three homoscalarane not only inhibited hypoxia induced HIF-1 activation with$IC_{50}$ of 0.64–6.9 μM, but also reduced the viability of T47D and MDA-MB- 231, the breast cancer cell lines. One of the homoscalarane confirmed the most potent active as unique tumor cell line selectivity to the NCI 60-cell line [40]. The manadic acids A and B as the fatty acids derivative have been isolated from the Indonesian sponge *Plakortis* sp. The evaluation of anticancer activity showed that both compounds moderately active against various tumor cell lines such as P388, A-549, HT 29, and MEL 28 with IC50 in the range of 0.5-5 μg/mL[41].

Indonesian *Plakortis nigra* have been yielded plakorstatins 1 and 2, exhibited the growth of the P388 lymphocytic leukemia cell line with $ED_{50}$ of 1.1 and 0.91 μg/mL, respectively [42].The most potential sponge from Indonesia *Theonella* cf. *swinhoei*, derived polyketide bitungolides A-F,that inhibit phosphatase VHR [43].

4. The potential anticancer compounds

Based on the publication between 1995-2020 on Indonesian marine sponge, there were several potential anticancer compounds in many groups such as alkaloid, terpenoid, steroid, peptide, polyketide, lipid, etc. Most of the anticancer compounds derived from the Indonesian marine sponges were alkaloid (23 compounds), while the others were steroid & terpenoid (16 compounds), peptide (8 compounds), and others (14 compounds). Anticaner compounds derived from Indonesian sponges with remarkable activity ($IC_{50}$ <1 μM or µg/mL) is described in table 1.
Table 1. Anticancer compounds derived from Indonesian Sponges with remarkable activity.

| Groups   | Compounds              | Cell Lines/enzyme inhibitor | IC50        | Source                           | References |
|----------|------------------------|----------------------------|-------------|----------------------------------|------------|
| Alkaloid | demethylaaptamine      | L5178Y (murine leukemia)   | 0.9 µM      | Aaptos suberitioides             | [20]       |
|          | Isoaaptamine           | P338 (murine leukemia)     | 0.28 µg/mL  | Aaptos sp                        | [22]       |
|          | 3-bromofascaplysin     | MALME-3M (the ubiquitin-activating enzyme) | 0.45 µM    | Fascaplysinopsis reticulata      | [30]       |
|          | Hyrtioreticulins A     |                            | 0.75 µg/mL  | Hyrtios reticulatus              | [32]       |
| Peptide  | Stylissamide X         | HeLa cells                 | 0.1 µM      | Stylissa sp                      | [37]       |
| Terpenoid| Sigmoid sceptrellin B  | L.5178Y                    | 0.55 µg/mL  | Diacarnus megaspinorhabdosa      | [18]       |
|          | Diacarpoxide S         | L.5178Y                    | 0.88 µg/mL  | Diacarnus megaspinorhabdosa      |            |

The structure of the potential compounds could be seen in Figure 1

![Figure 1](image1.png)

**Figure 2.** The structure of potential compounds: demethylaaptamine (1), isoaaptamine (2), Hyrtioreticulins A (3), stylissamide X (4)

The hydroxyl group of demethylaaptamine (1) plays an important role in the anticancer activity, methylation of this group decreased the activity [20]. Isoaaptamine showed strong activity against murine leukemia cell line P338. The para substitution of a phenyl ring attached via an ester linkage to the hydroxyl position of isoaaptamine (2) determined the selectivity toward the target [22]. Hyrtioreticulins A (3), also showed strong inhibition toward the E1-ubiquitin intermediate formation in a dose-dependent manner with IC_{50} values of 0.75 µg/mL. The imidazole moiety attached in C1 and trans position plays an important role in inhibiting E1 enzyme [32].

Cyclic peptides such as several compounds isolated from marine origin including stylissamide X (4) have been reported active as anti-infective and anticancer [37].

5. Conclusion

In conclusion, The Indonesian marine sponges derived the potential anticancer compounds such as demethylaaptamine, Isoaaptamine, 3-bromofascaplysin, 3-bromofascaplysin, Hyrtioreticulins A,
Styliassamide X, Sigmosceptrellin B Sigmosceptrellin B, and Diacarperoxide. Most of them were identified from the alkaloid group. Further investigation such as in silico studies is needed to find more structure-function information and specific target receptor.

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