TINJAUAN BAHAN ALAM MAKROALGA DI INDONESIA: STATUS DAN POTENSIAL

REVIEW: MACROALGAE NATURAL PRODUCT IN INDONESIA, THE STATUS AND POTENTIAL

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Abstrak – Potensi sumberdaya kelautan Indonesia sangatlah besar ditunjang oleh keanekaragaman biologi dan kimia (biochemo-diversity) untuk penemuan berbagai bahan alam yang dapat dimanfaatkan sebagai sumber bahan farmasi, nutrisi, maupun bahan baku industri lainnya. Tinjauan ini akan memaparkan sejarah bahan alam laut, lalu diikuti dengan deskripsi kekayaan biologi dan kimiawi Indonesia dari organisme laut, dan diakhiri dengan uraian tentang status dan potensi bahan alam dari makroalga Indonesia. Sudah terdapat minimal enam bahan alam yang sudah secara komersil sebagai antivirus, anti cancer, dan anti HIV. Sejak awal dekade 90-an, terdapat beberapa bahan alam laut Indonesia yang berasal dari organisme seperti, spons, intertebrata laut, maupun jamur. Makroalga laut masih menyimpan potensi lebih jauh karena eksplorasi yang masih terbatas pada zona intertidal.
Kata Kunci: Bahan alam laut, Biokimia diversitas, Makroalga

Abstract *– The potential of Indonesia's marine resources is very vast, supported by biological and chemical diversity (biochemo-diversity), for the discovering of various natural materials that can be used as a source of pharmaceutical, nutritional, and other industrial raw materials. This review will describe the history of marine natural materials, followed by a description of Indonesia's biological and chemical richness of marine organisms, and ends with a description of the status and potential of Indonesian macroalgae natural products. There are already at least six natural products that have been commercially used as antiviral, anti-cancer, and anti-HIV. Since the early 90s, there have been several Indonesian marine natural materials derived from organisms such as sponges, marine invertebrates, and fungi. Marine macroalgae still have further potential because exploration is still limited to the intertidal zone.*
Keywords*: Biochemo diversity, Macroalgae, Marine natural products*

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I. INTRODUCTION

Natural products as lead compounds have mainly come from terrestrial plants and microbes as they are widely accessible to collect (Molinski et al. 2009). An effort to explore the medicinal potential of marine natural products (MNPs) was first detailed at a conference in Rhode Island, USA, in the 1970s. Improved sampling methods, e.g., SCUBA apparatus, has contributed significantly to the progress of discovery new MNPs, not to mention the development of spectroscopy technology and screening protocols.(Faulkner 1984) As a result, the number of new marine natural products has increased from 332 in 1984(Blunt et al. 2017) to 1340 in 2016.(Bergmann & BURKE 1955) New compounds have been isolated from marine organisms in subtidal and intertidal zones including micro and macroalgae, littoral plants, various invertebrates (poriferans, anthozoan, bryozoans, mollusks, tunicates, echinoderms, and bacteria) (Bergmann & BURKE 1955).

The first MNPs were reported in 1951 when two nucleosides, spongothymidine and spongouridine, were extracted from the Caribbean sponge *Tethya crypta* (Bergmann & Feeney 1951, Suckling 1991). These compounds led to three drugs, which have anti-viral (Ara-A, commonly known as Vidarabine), anticancer (Ara-C also known as Cytosar-U), and anti-HIV activities (azido thymidine-AZT) (Newman & Cragg 2004, Montaser & Luesch 2011). In fact, both Ara-C or Cytarabine and Ara-A were the first MNP-derived drugs approved by the FDA in 1969 and 1976, respectively (McGivern 2007). However, ziconotide, a ω-conotoxin MVIIA (25 amino acid peptide chain) was the first FDA approved drug extracted and isolated directly from its source, the Indo-Pacific marine snail *Conus magus* (Olivera 2000, Somaiah & von Mehren 2012).

Currently, there are six FDA approved MNPs drugs including the aforementioned drugs, trabectedin (Yondelis) and eribulin mesylate (Newman & Cragg 2004, 2012). Trabectedin, a tris (tetrahydroisoquinoline) alkaloid, was isolated from *Ecteinascidia turbinata* and is used for the treatment of non-operable soft tissue sarcomas (Somaiah & von Mehren 2012). Eribulin mesylate is a synthetic analogue of halichondrin B, extracted from the Japanese sponge *Halichondria okadai*, and is an FDA-approved treatment for metastatic breast cancer (Mayer et al. 2010).

Despite only a small number of MNPs drugs being approved, many of them are still in clinical trials (Arifin & Nakagoshi 2011), which still provides huge potential for development. At present, there are five compounds in phase III clinical trials, which come from fungi, pufferfish, tunicates, and mollusks. Also, there are ten and six compounds in phase II and I clinical trials respectively, which most of them are coming from mollusks. Most of these compound target a variety of cancers (an updated list of current marine-derived compounds on the drug pipeline is available on the following website: http://marinepharmacology.midwestern.edu/clinical_pipeline.html).

II. INDONESIA BIODIVERSITY AND MARINE NATURAL PRODUCTS

Indonesia has been privileged with the world's third most mega-biodiversity, according to the United Nations Environment Programme-UNEP (Arifin & Nakagoshi 2011). It has 47 ecosystem types, ranging from ice fields and alpine meadows to coral-reefs, with approximately 17% of the total number of species in the world found in Indonesia (Strid 1997).

Regarding marine biodiversity, Indonesia lies at the heart of the Coral Triangle region

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(part of Coral Triangle Initiative[†]) which consists of 43,682 square kilometers of coral reef spanning from the Philippines in the north to the Solomon Islands in the south. Nearly 50 percent (19,868 sqkm) of the area is located in Indonesia, providing habitats for 500 species of coral (18 percent of the world's coral reefs) and 5,000 species of fish and mollusca on top of numerous marine plant species (Huffard et al. 2012). For this reason, it has attracted many researchers to examine the full potential of marine biodiversity in Indonesia.

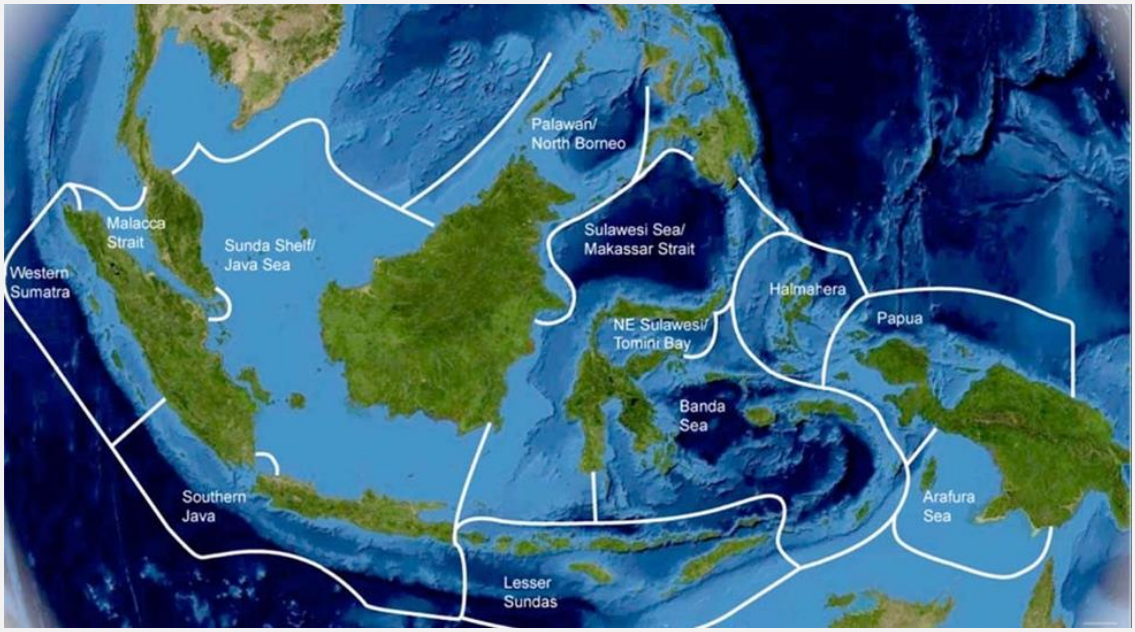

Figure 1. Map showing the twelve Indonesia marine ecoregions as defined in the Marine Ecoregions of the World classification scheme(Veron et al. 2009, Huffard et al. 2012, White et al. 2014)

Marine natural products research in Indonesia has captured research attention mainly in the period between 2002 and 2003, as well as 2012-2013. However, the first reported paper of MNPs in Indonesia was in 1974 when tricyclic (+)-africanol (**18**, Figure 2) was isolated from the soft coral *Lemnalia africana* (Leti Island, Maluku) (Tursch et al. 1974).

[†]Coral Triangle Initiatives consist of six nations: Indonesia, Malaysia, the Philippines, Papua New Guinea, the Solomon Islands and Timor Leste

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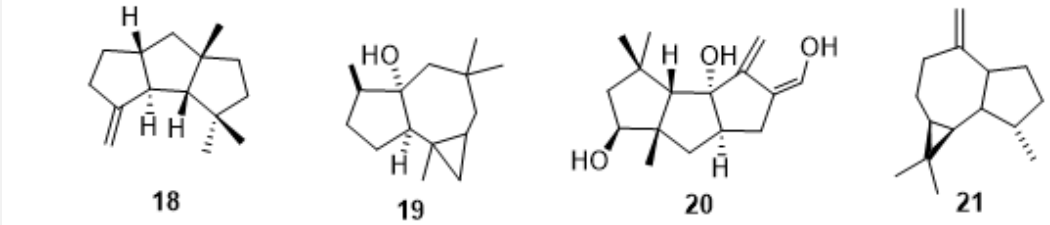

Figure 2. Chemical structure of (+)-africanol (**18**), Δ9(12)-Capnellene sesquiterpenes (**19**), (+)-Δ9(12)-capnellene-3ß,8ß,10α,14ß-tetraol (**20**), and aromadendrene (**21**)

Later that decade, a few researchers had also reported their findings from another soft coral genus *Capnella* as sources of Δ9(12)-capnellene sesquiterpenes (Ayanoglu et al. 1978) (**19**, Figure 2), while tetraol (+)-Δ9(12)-capnellene-3β,8β,10α,14β-tetraol (**20**, Figure 2) was found from a specimen collected at the same location in 1977 (Sheikh et al. 1977). Another group reported that they successfully isolated aromadendrene (**21**, Figure 1.6) from the soft coral *Sinularia mayi* (from Nias Island) in 1978 (Beechan et al. 1978).

Table 1. Marine natural product from sponges

No	Species	Compound and bioactive	Location	Literature
1.	*Sidonops microspinosa*	Microspinosamide: inhibits cytopathic effect of HIV-1 infection	South East Sulawesi	(Rashid et al. 2001)
2.	Family Petrosiidae	Manzamine: 8-hydroxymanzamine A, manzamine F, along with the unprecedented manzamine dimer, *neo*-kauluamine. They show antimaria activity against *Plasmodium berghei*	North Sulawesi	(El Sayed et al. 2001)
3.	*Theonella swinhoei*	Bitungolides A–F; Dual-specificity against phosphatase VHR	North Sulawesi	(Sirirath et al. 2002)
		Aurantoside F-J are a new compound and showed a detectable antifungal activity	North Sulawesi	(Angawi et al. 2011)
4.	*Haliclona* sp.	Brominated fatty acid showed moderate cytotoxicity against rat bladder epithelial cells)	Alor Island, East Nusa Tenggara	(Aratake et al. 2009) (Aoki et al. 2002a) (Trianto et al. 2011)

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No	Species	Compound and bioactive	Location	Literature
		Acetylene alcohols: lembehynes B and C. It showed neuritogenic activity against neuroblastoma cells	South Sulawesi	
		Halioxepine showed moderate cytotoxicity against NBT-T2 cells and antioxidant activity	Buton Island, Southeast Sulawesi	
5.	*Hyrtios reticulatus* and *Hyrtios erectus*	1,6-dihydroxy-1,2,3,4-tetrahydro-β-carboline; hyrtiosulawesine	South Sulawesi	(Salmoun et al. 2002)
6.	*Hippospongia* sp.	Sesterterpenoid: barangcadoic acid A and rhopaloic acids A	South Sulawesi	(Craig et al. 2002)
7.	*Phyllospongia* sp.	Scalarane sesterterpenoids	South Sulawesi	(Roy et al. 2002)
8.	*Petrosia strongylata*	Sulfated sterols: lembehsterols A-B show inhibitory activity against thymidine phosphorylase (angiogenesis in solid tumors)	North Sulawesi	(Aoki et al. 2002b)
9.	*Callyspongia pseudoreticulata*	Diyne which is toxic to brine shrimp assay	South Sulawesi	(Braekman et al. 2003)
10.	*Melophlus sarassinorum*	Tetramic acid: melophlin C is an antimicrobial active against *Bacillus subtilis* and *Staphylococcus aureus*, also antifungal against *Candida albicans*, while melophlins D–O (less active)	South Sulawesi	(Wang et al. 2003)
11.	*Sigmadocia symbiotica* (symbiont with alga *Ceratodictyon spongiosum*)	*Ceratospongamide: cis,cis*- and *trans,trans*- isomers antiinflammation and inhibit the expression of a human-sPLA$_2$promoter-based reporter	Biaro Island, South Sulawesi	(Tan et al. 2000)
12.	NA	Manzamine alkaloids which has bioactivity against malaria, TB, and leishmaniasis	South Sulawesi	(Rao et al. 2003)
13.	*Fascaplysinopsis reticulate*	3-bromofascaplysin, 14-bromoreticulatine, and 14-bromoreticulatate	Indonesia	(Segraves et al. 2003)
14.	*Biemna fortis*	Labuanine is a neuronal differentiation inducer against neuroblastoma	West Flores, East Nusa Tenggara	(Aoki et al. 2003)
15.	*Xestospongia* sp.	Aaptamine antibacterial against *S. aureus*, *E. coli*, *V. anguillarum*; also antifungal against *C. tropicalis*)	Jakarta	(Calcul et al. 2003)

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No	Species	Compound and bioactive	Location	Literature
16.	*Stylissa carteri*	Oroidin: latonduines A-B	Latondu Island, South Sulawesi	(Linington et al. 2003)
17.	*Hyrtios* sp.	Merosesquiterpenes: puupehenone	North Sulawesi	(Piña et al. 2003)
18.	*Axinyssa aculeate* (also its mollusk nudibranch predator *Phyllidia varicose*)	Sesquiterpenoids: 9-thiocyanatopupukeanane which weakly and moderately antifungal against *B. subtilis* and *C. albicans*	Thousands Island, Jakarta	(Yasman et al. 2003)
19.	*Plakortis* cfr. *lita*	Plakortin, manadoperoxides A–D and peroxyplakoric ester B3. Show antiprotozoal activity against *Trypanosoma brucei rhodesiense*	North Sulawesi	(Chianese et al. 2012)
20.	*Stylissa* sp.	Octapeptide stylissamide which inhibit HeLa cell migration	Biak, Papua	(Arai et al. 2012)
21.	*Acanthostrongylophora* sp.	Acantholactone	North Sulawesi	(Wahba et al. 2012)
22.	*Hyrtios reticulatus*	Hyrtioreticulins A against the formation of an E1-ubiquitin activating enzyme inhibitor	North Sulawesi	(Yamanokuchi et al. 2012)
23.	*Stylissa* sp.	Stevesines cytotoxicity against mouse lymphoma cell line and debromolatonduines	Derawan Island, East Kalimantan	(Fouad et al. 2012)
24.	*Aplysinella strongylata*	19-Hydroxypsammaplysin E showed modest inhibition of chloroquine-sensitive *P falciparum*	Bali	(Mudianta et al. 2012)
25.	*Lissodendryx fibrosa*	Sterols: manadosterols A and B, both showed potential as anticancer agents	North Sulawesi	(Ushiyama et al. 2012)
26.	*Plakortis lita*	hopanoid glycoside: plakohopanoid	North Sulawesi	(Costantino et al. 2012)
27.	*Acanthostrongylophora* sp.	Manzamine-type alkaloids: 12,28-oxamanzamine E, 12,34-oxa-6-hydroxymanzamine E, 8-hydroxymanzamine B and 12,28-oxaircinal. They are showed significant inhibitory enzyme implicated in Alzheimer's disease pathology	North Sulawesi	(Rao et al. 2006)
28.	*Coelocarteria cfr.singaporensis*	*Ent*-isocopalane diterpenes: coelodiol and coeloic acid. Inhibit human gastric adenocarcinoma	North Sulawesi	(Fattorusso et al. 2006)

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No	Species	Compound and bioactive	Location	Literature
29.	*Corticium simplex*	Steroidal Alkaloids: Cortistatins A-D, an anti-angiogenic activity	Flores Island, East Nusa Tenggara Indonesia	(Aoki et al. 2006)
30.	*Dactylospongia elegans*	Furanosesterterpene: Furospinosulin-1, an antiproliferative activity against human prostate cancer and antitumor activity		(Arai et al. 2010)
31.	*Rhabdastrella globostellata*	Globostellatic acids A and D and stelliferin riboside; new natural products. They show selectively active against mouse lymphoma cell	Kapoposang Island, South Sulawesi	(Fouad et al. 2006)
32.	*Xestospongia cf. vansoesti*	Salsolinol and its derivates norsalsolinol, cis-4-hydroxysalsolinol, and trans-4-hydroxysalsolinol. Show inhibition activity against chymotrypsin	North Sulawesi	(Nagasawa et al. 2011)
33.	*Dasychalina* sp.	Desulfohaplosamate that is a selective cannabinoid CB2-receptor ligand	South Sulawesi	(Chianese et al. 2011)

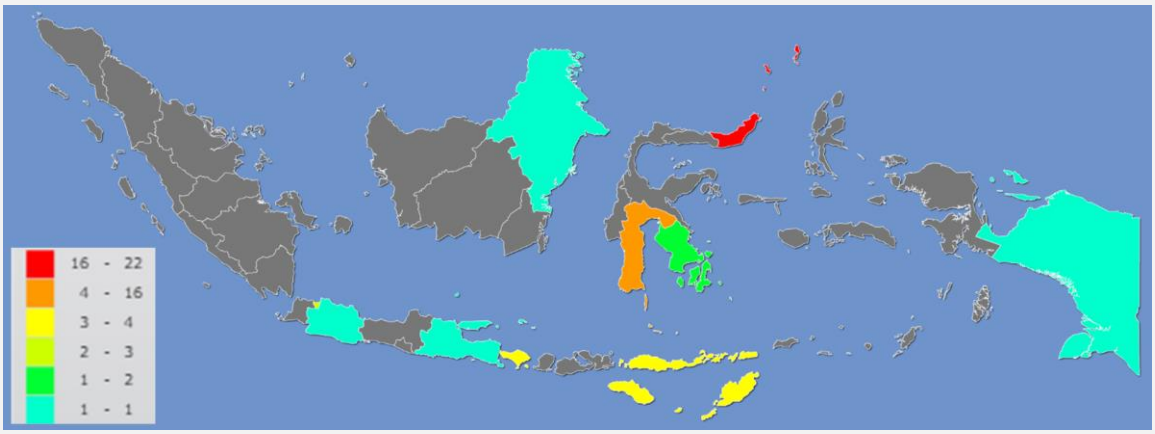

Figure 3. Frequency of marine natural products research from new and novel compound from Indonesia based on provinces (see Appendix A for the details); the number indicates total papers published.

A

mong marine species, sponges have been the richest sources of bioactive compounds from Indonesia, comprising almost 60% of total research covered in this introduction chapter, followed by fungi, tunicates, and other invertebrates (Figure 3; Table 1-3). Most of the research has been done in Sulawesi Island especially North and South Sulawesi Provinces which accounted for 22 and 16 published papers, respectively.

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Table 2. Marine natural products from fungi

No	Species	Compound and bioactive	Location	Literature
1.	*Curvularia lunata* (symbiont with sponge *Niphates olemda*)	Lunatin antibacterial against *S. aureus*, *E. coli* and *B. subtilis* but inactive against *C. albicans*	Bali	(Jadulco et al. 2002)
2.	*Cladosporium herbarum (*symbiont with sponge *Callyspongia aerizusa)*	Phthalide herbaric acid show no activity; furan show activity against *Bacillus subtilis* and *Staphylococcus aureus*	Bali	(Jadulco et al. 2002), (Jadulco et al. 2001)
3.	*Penicillium cf. montanense* from sponge *Xestospongia exigua*	Xestodecalactones A–C but only xestodecalactones B active against *C. albicans*	Bali	(Edrada et al. 2002)
4.	*Myrothecium* sp. From unidentified sponge	Trichothecenes: roridin R cytotoxic to L1210 cells	North Sulawesi	(Xu et al. 2006)
5.	*Aspergillus sp.* from unidentified alga	Hexahydroanthrones: tetrahydrobostrycin and 1-deoxytetrahydrobostrycin. Both show weak antibacterial activity against *Staphylococcus aureus* and 1-deoxytetrahydrobostrycin also against *Escherichia coli*	North Sulawesi	(Xu et al. 2008)
6.	Endophytic *Daldinia eschscholzii* from alga *Gracilaria sp.*	Lactone, antifungal against *Cladosporium cucumerinum*	South Sulawesi	(Tarman et al. 2012)
7.	Unidentified fungi from unknown alga	Naphthalene, fungicidal against *Cladosporium cucumerinum*	East and West Java, and North Jakarta	(Tarman et al. 2011)
8.	Unidentified fungi from unknown sponge	Hexaketide: *iso*-cladospolide B, *seco*-patulolide C; Macrolides: pandangolide 1 and pandangolide 2, cladospolide B	South Sulawesi	(Smith et al. 2000)

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Table 3. Other group of marine natural products from invertebrate (dinoflagellate, cyanobacteria bacteria, coelenterates, tunicates, cnidarian)

No	Species	Compound and bioactive	Location	Literature
1.	*Amphidinium* sp. as symbiont of marine flatworm	Polyols: karatungiols A and B howed antifungal activity against *Aspergillus niger* and antiprotozoan activity against *Trichomonas foetus*	North Sulawesi	(Washida et al. 2006)
2.	*Phormidium* sp.	Phormidolide, show activity against brine shrimp tocix	Sulawesi Island	(Williamson et al. 2002)
3.	*Streptomyces* sp.	komodoquinone A dose-dependent neuritogenic activity against the neuroblastoma cell and B	Komodo Island, East Nusa Tenggara	(Itoh et al. 2003)
4.	Xenia sp.	xeniolide F and 9-hydroxyxeniolide F	North Sulawesi	(Anta et al. 2002b)
5.	*Pachyclavularia violacea*	Sterols: ecosterol	North Sulawesi	(Anta et al. 2002a)
6.	*Isis hippuris*	polyoxygenated sterols	Sulawesi Island	(González et al. 2001)
7.	*Didemnum* sp.	(+)-didemniserinolipid B then revised as 31-sulfate	South Sulawesi	(González et al. 1999), (Kiyota et al. 2002)
8.	*Eusynstyela latericius*	Hydroxylpyridoacridine alkaloid: styelsamine C	South Sulawesi	(Copp et al. 1998)
9.	*Leptoclinides dubius*	Leptoclinidamide and (*R*)-leptoclinidamine B	North Sulawesi	(Yamazaki et al. 2012)
10.	*Cladiella* sp.	6-hydroxyeunicellin diterpenoids, cladieunicellin G and 6-epi-cladieunicellin F	Indonesia	(Chen et al. 2012)
11.	*Sinularia* sp.	Llkaloids: sinulasulfoxide and sinulasulfone. Sinulasulfoxide proved to moderately inhibit LPS-induced NO release	North Sulawesi	(Putra et al. 2012b)
		Sterols: gorgosterol	North Sulawesi	(Putra et al. 2012a)
		norcembranes chloroscabrolide A and B	North Sulawesi	(Fattorusso et al. 2011)

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Two new sesquiterpenoids, boneratamides-A (**22**) boneratamides-B (**23**, Figure 4), have been isolated from the marine sponge *Axinyssa aplysinoides* collected in South Sulawesi (Williams et al. 2004). A few secondary metabolites were isolated from North Sulawesi sponges, for example a peptide, microspinosamide (**24**, Figure 4), which contains 13 amino acid residues, was isolated from *Sidonops microspinosa* (Rashid et al. 2001).

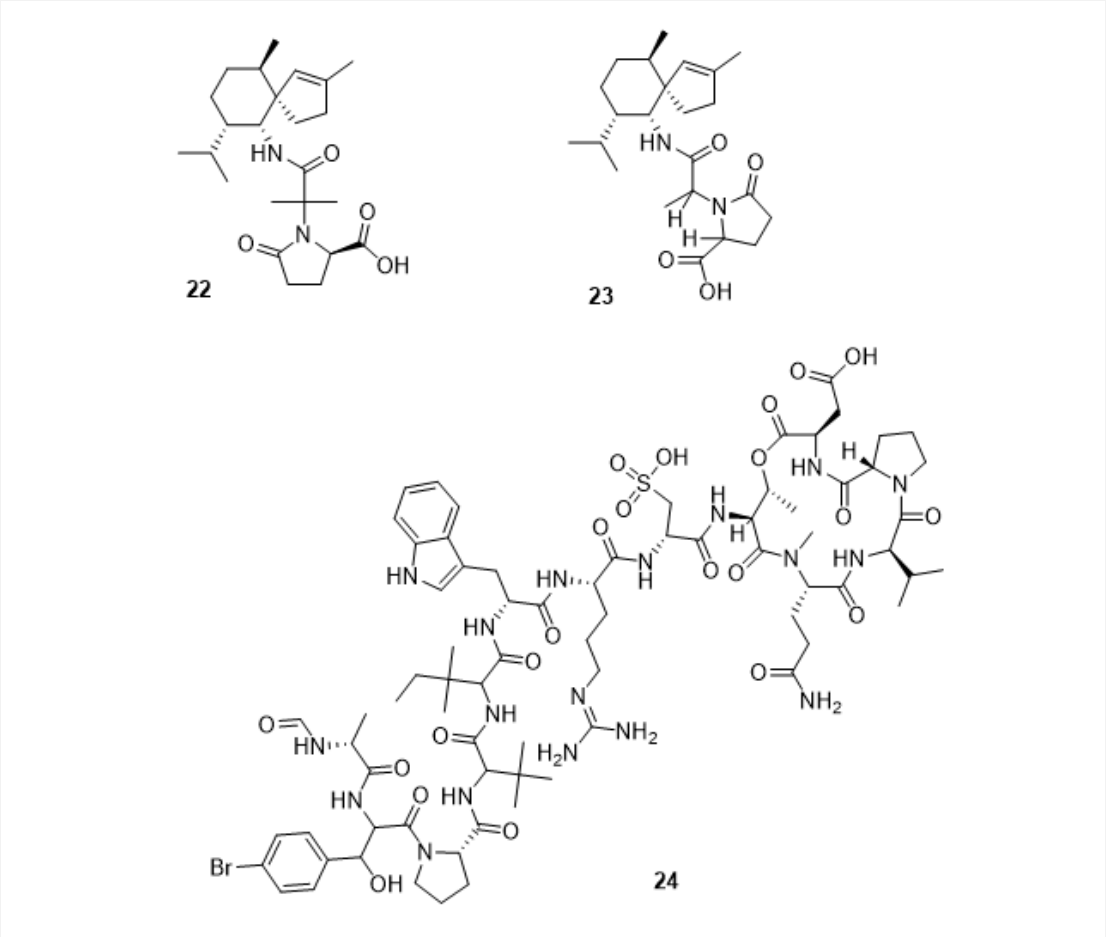

Figure 4. Chemical structure of boneratamides-A (**22**), boneratamides-B (**23**), microspinosamide (**24**)

Both organic and aqueous extracts of microspinosamide showed anti-HIV-1 activity at a concentration of 0.12 μM (Rashid et al. 2001). Other metabolites, manadomanzamines A (**25**) and B (**26**, Figure 5) isolated from *Acanthostrongylophora* sp., were also showed activity against HIV-1 with EC_{50} values of 11.5 and 27.0 μM respectively (Peng et al. 2003). Manadomanzamines also exhibited strong activity against *Mycobacterium tuberculosis* (Somei & Yamada 2005). Two new imidazole alkaloids, naamidines H (**27**, Figure 5) and I (**28**, Figure 5), were isolated from the marine sponge *Leucetta chagosensis* (Tsukamoto et al. 2007) (see Table 1-3 for a complete list of MNPs research in Indonesia).

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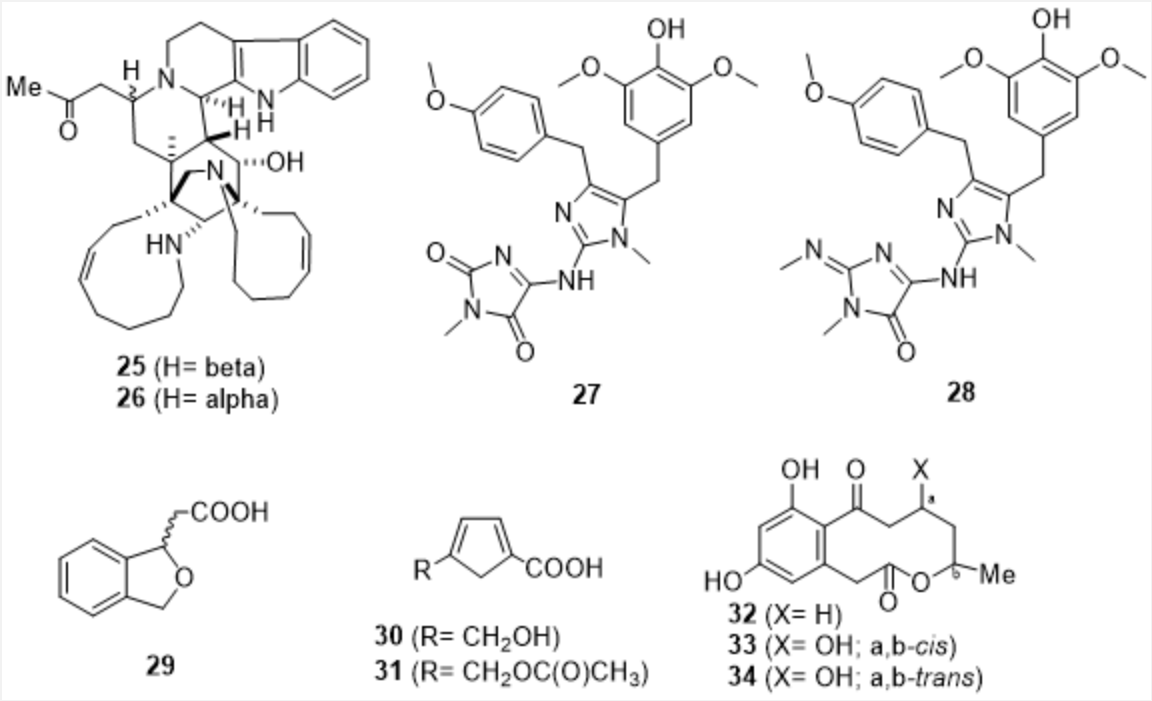

Figure 5. Chemical structure of manadomanzamines A (**25**), manadomanzamines B (**26**), naamidines H (**27**), naamidines I (**28**), herbaric acid (**29**), Sumiki's acid (**30**), acetyl Sumiki's acid (**31**), xestodecalactones A, B, and C (**32-34**)

Furthermore, two metabolites were isolated from *Cladosporium herbarum* (symbiont of the sponge *Callyspongia aerizusa*) namely, a new phthalide herbaric acid (**29**, Figure 5), which showed no activity, and furan carboxylic acids: Sumiki's acid (**30**) and acetyl Sumiki's acid (**31**, Figure 5), which both showed activity against *Bacillus subtilis* and *Staphylococcus aureus* (Jadulco et al. 2001). Another fungus collected from Bali, *Penicillium cf. montanense*, also extracted from a sponge (*Xestospongia exigua*), is a 10-membered macrolides with a fused 1,3-dihydroxybenzene ring xestodecalactones A–C (**32–34**, Figure 5), of which only (**33**) was active against *C. albicans* (Edrada et al. 2002).

III. MACROLAGAE NATURAL PRODUCTS

Commonly known as seaweed, marine macroalgae has historically been sources of edible seaweed (MacArtain et al. 2007) and raw materials for primary metabolites including gelatin, gellan, pectin, agar, carrageenan, and alginate (Saha & Bhattacharya 2010). Edible seaweed has been consumed primary by Asian cultures, where species such as brown algae (*Fucus vesiculosus*, Kombu-*Laminaria digitate*, and Wakame-*Undaria pinnatifida*) and red seaweeds (Nori-*Porphyra tenera*) have been commercially produced. Algae have been utilized to more extensive food products, for example jam, cheese, wine, tea, soup and noodles in Japan (Nisizawa et al. 1987). The hydrocolloidal properties of seaweed are exploited as thickening agents and gelling agents in various uses such as salad dressings, sauces and toppings, jelly, marmalade, restructured foods and low sugar/calorie gels (Glicksman 1987, Saha & Bhattacharya 2010).

Macroalgae are found as sessile organisms in intertidal habitats, which is the area between high and low tides. Therefore make marine macroalgae are exposed periodically to both biotic and abiotic stressors (Hay 1981, Davison & Pearson 1996, Stachowicz 2001). The stresses range from herbivorous fish predation,

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competition, and disease to various environmental conditions (high and low temperature, desiccation, and osmotic stress) (Davison & Pearson 1996). Active compound defences are used to fight against pathogens and bio-foulants (Lane & Kubanek 2008), colonization/biofilms on seaweeds and bacterial signalling (Steinberg & De Nys 2002, Maschek & Baker 2008). The various ecological situations force macroalgae to develop a chemical defence mechanism through production of bioactive secondary metabolites. This fact along with their ubiquitous and accessible habitats led natural products chemists into study marine macroalgae as the first group amongst other marine organisms.

The classification of secondary metabolits from macroalgae is derived from their biosynthetic origin. Terpenes are the largest and most diverse class of compounds derived from macroalgae. Terpenes, of which the name can be used interchangeably with terpenoids, make up approximately half of the active compounds found from algae (Maschek & Baker 2008). Together with polyketides, amino acid derivatives (including non-ribosomal peptides and simple amino acid derivatives), and alkaloids, they encompass almost a quarter of known algae active compounds. Shikimates, usually found in aromatic natural products, are the next largest group of natural products, and the last group consists of various classes of secondary metabolites that are infrequently found in macroalgae, such as nucleosides and other classes of compounds bound to sugars.

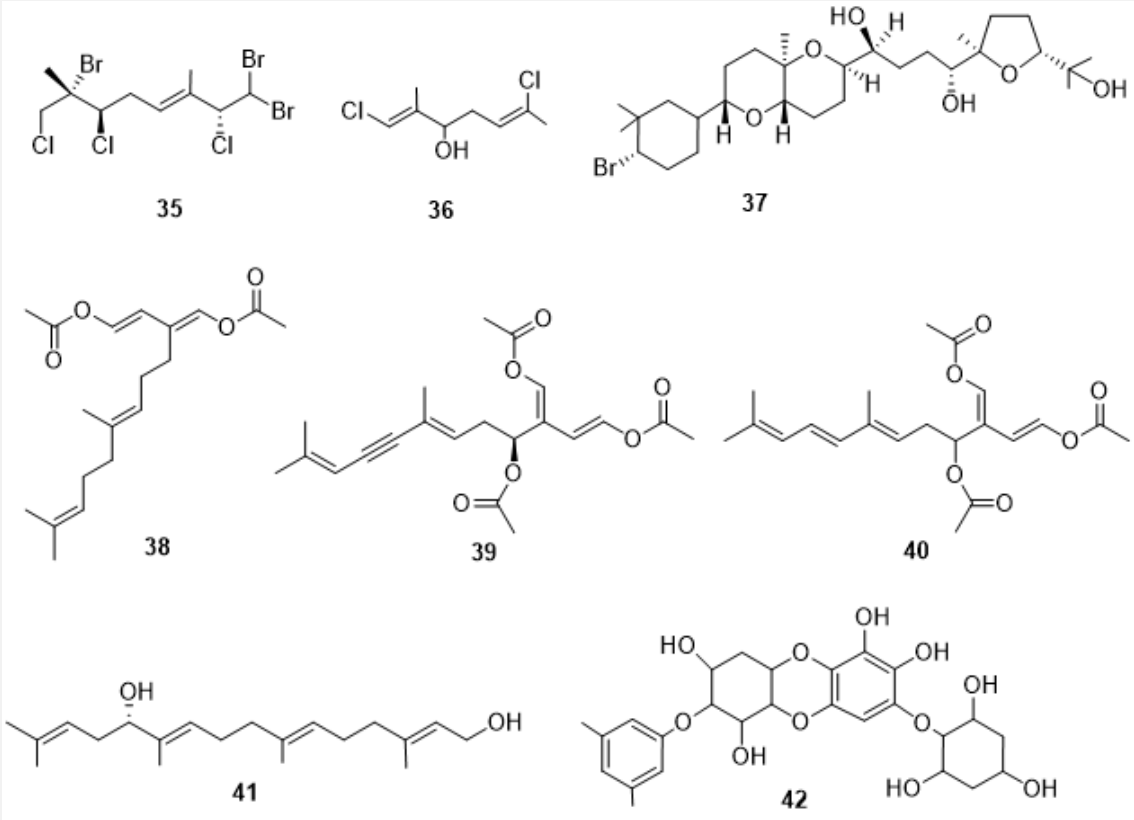

Figure 6. Chemical structure of Chemical structure of polyhalogenated monoterpene (**35**), bisnormonoterpenoid (**36**), thyrsiferol (**37**), flexilin (**38**), caulerpenyne (**39**), rhipocephalin (**40**), (S)-12-hydroxygeranylgeraniol (**41**), and diphlorethohydroxycarmalol (**42**)

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The first study of red algae was reported by Blunt and co-workers, who isolated a polyhalogenated monoterpene (**35**, Figure 6) and a bisnormonoterpenoid (**36**, Figure 6) from *Plocamium cruciferum* in 1978 (Blunt et al. 1978b). Also, they found the uncommon squalene derived metabolite, thyrsiferol (**37**, Figure 6), from the red alga *Laurencia thyrsifera* (Blunt et al. 1978a). Early studies found the simplest form of 1,4-diacetoxybutadiene in a green algae sample, namely flexilin (**38**, Figure 6) isolated from *Caulerpa flexilis* in 1978 (Blackman & Wells 1978). Two metabolites, caulerpenyne (**39**, Figure 6) and rhipocephalin (**40**, Figure 6), were isolated from *Caulerpa prolifera* and *Rhipocephalus phoenix*, respectively. Meanwhile, secondary metabolites from brown algae are predominantly terpenes and polyphenols. For example, the diterpene (S)-12-hydroxygeranylgeraniol (**41**, Figure 6) was isolated from the brown alga *Bifurcaria bifurcate* collected off the Atlantic coast from Morocco (Culioli et al. 2001), and diphlorethohydroxycarmalol (DPHC) (**42**, Figure 6) was isolated from *Ishige okamurae*, collected along the coast of Jeju Island, Korea (Heo et al. 2009). DPHC was shown to be active against postprandial hyperglycemia in diabetic mice, as well as a potent α-glucosidase and α-amylase inhibitor.

IV. INDONESIA MACROALGAE

Indonesia is one of the richest countries in the world for marine species. About 45% of the world's marine algae species are found in Indonesia, including 196 green algal species, 134 brown algal species, and 452 red algal species (Kasanah et al. 2015). Algae species are mainly spread across the central and eastern parts of Indonesia such as Sulawesi, Bali, Nusa Tenggara, and Maluku. Due to this high diversity of marine macroalgae, eastern parts of Indonesia are commonly referred to as "the barn of seaweed." However, according to the algaebase database (http://www.algaebase.org), less than one percent of marine algae have been reported from Indonesia (out of more than 360,000 records of known algae worldwide) (Guiry 2017).

Owing to this highly abundant resource, the phycocolloid industry produces polysaccharide compounds (primary metabolite) from seaweed and has been established in Indonesia to support many coastal communities around those aforementioned areas. A few important species that have been cultivated, namely *Kappaphycus alvarezii*, *Eucheuma* spp., and *Gracilaria* sp, are the major contributors to dry seaweed production in Indonesia. In fact, Indonesia has been the largest producer of seaweed farming since 2014 when its share of global production increased dramatically from 6.7 percent in 2005, to 36.9 percent (FAO 2016). However, little attention has been given to Indonesian algae as a source of pharmacological supply, and only a few studies have been conducted on this topic in Indonesia. Most of the research has conducted focused on red algae species, for example, *Vidalia* sp. and *Gracilaria asiatica* which a phenolic vidalenolone (**43**, Figure 7) and a cyclopropyl gracilarioside (**44**, Figure 7) respectively, isolated from these algae (Yoo et al. 2002, Sun et al. 2006). Gracilarioside was found to be mildly cytotoxic to the human A375-S2 melanoma cell line.

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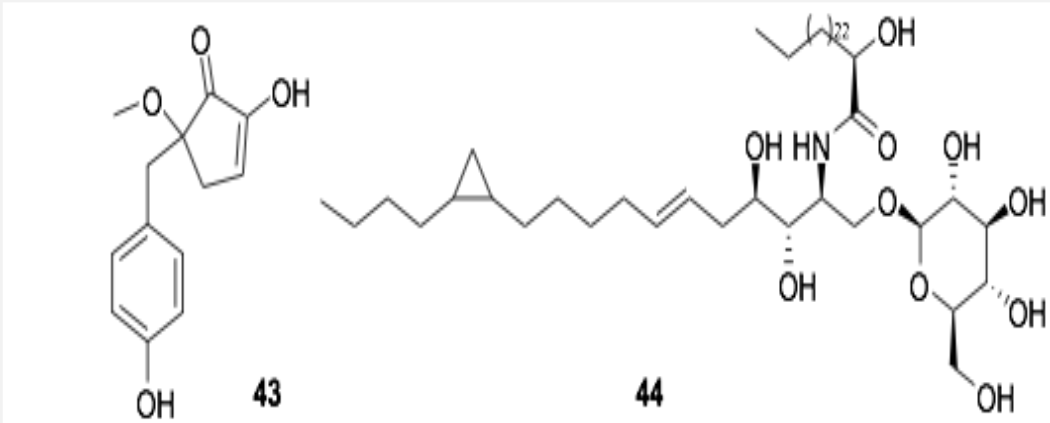

Figure 7. Chemical structure of vidalenolone (**42**) and gracilarioside (**44**)

One of the most significant issues in marine pharmacological research is the supply of raw materials. Even production of active metabolits on the gram scale is difficult to achieve from natural sources (Newman & Cragg 2004). Therefore, most of the clinical investigations from marine secondary metabolites are supplied from chemical synthesis (Bowling et al. 2007). This problem may be addressed by a greater supply of macroalgae. Once a novel compound has been isolated from macroalgae, the abundance of naturally-occurring macroalgae in Indonesia could support the industry, especially for drug discovery purposes. Furthermore, already established seaweed farms in Indonesia may also sustain this industry from the supply side and best farming practices.

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