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Article

Indonesian marine biodiversity as a sustainable resource to support Indonesian pharmaceutical industry in ASEAN pharmaceutical market

The International Journal of Management Science and Information Technology (IJMSIT)

Provided in Cooperation with:

North American Institute of Science and Information Technology (NAISIT), Toronto

Suggested Citation: Riandy, Andika Putra; Handayani, Alvionita (2015) : Indonesian marine biodiversity as a sustainable resource to support Indonesian pharmaceutical industry in ASEAN pharmaceutical market, The International Journal of Management Science and Information Technology (IJMSIT), ISSN 1923-0273, NAISIT Publishers, Toronto, Iss. 18, pp. 20-24

This Version is available at:

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An official publication of The North American
Institute of Science and Information Technology

ISSN:1923-0265

INTERNATIONAL JOURNAL OF

Management Science and Information Technology



NAISIT
PUBLISHERS **III**

www.naisit.org

The International Journal of Management Science and Information Technology (IJMSIT)

NAISIT Publishers

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NAISIT Publishers

Special Issue: 14th Indonesian Scholars International Convention

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This is one paper of
The International Journal of Management Science and
Information Technology (IJMSIT)
Special Issue: 14th Indonesian Scholars International
Convention

INDONESIAN MARINE BIODIVERSITY AS A SUSTAINABLE RESOURCE TO SUPPORT INDONESIAN PHARMACEUTICAL INDUSTRY IN ASEAN PHARMACEUTICAL MARKET

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ABSTRACT

Indonesian waters are known as mega-diversity resource which can produce many chemical compounds. These compounds have been identified could be a sustainable source for novel drugs, especially for the usage of pharmaceutical. Up to 2007, at least 77 new compounds are from 14 sponges and 19 new compounds are from non-sponge organisms with pharmacological potential have been identified from Indonesian waters. Unfortunately, this richness is not optimized yet. By the literature survey methods, marine culture might be one of the methods which can be developed in Indonesia to overcome the degradation hazard of marine resources. Through this method, Indonesia could be a great nation with the huge of resources for domestic and ASEAN pharmaceutical industry which can provide economic value for Indonesia and also can strengthen Indonesia in facing ASEAN pharmaceutical market.

Keywords: Indonesia, Mari culture, pharmacological potential

1. INTRODUCTION

Indonesia is known as archipelagic country, a country with 17,508 islands which stand on a very strategic geographic, because it is a cross position, i.e. between the continents of Asia and Australia and between the Indian Ocean and the Pacific. The sea and the strait become a connector of those islands, and based on national jurisdiction is an archipelago country with length 5.110 km and width of 888 km, 5,877,879 km² is the surroundings waters area, the territorial sea area about 297 570 km², the waters Exclusive Economic zone (EEZ) about 695 422 km², 79 610 km is long beach, where two-thirds of them is the area of sea and onshore i.e. 2,001,044 km² (Pussurta TNI, 2001). Indonesia is bordered with many countries, both on the land area and the sea area. Indonesia's land is bordered with three countries, namely Malaysia (West Kalimantan and East Kalimantan to Sarawak and Sabah), the province of Papua to Papua New Guinea and East Nusa Tenggara to Timor Lorosae. In the sea area, Indonesia is bordered with ten countries. They are India, Thailand, Malaysia, Singapore, Vietnam, Philippine, Palau, Papua New Guinea, Australia and Timor Lorosae. Indonesia is one of the ten countries with the richest biodiversity, and is often known as a mega-diversity country (Anonymous, 2003). In more than 20 years, Indonesia has become a target for bioactive marine natural product chemistry research, and there are a lot novel compounds and scientific papers which have been published as cited in the following section. The uniqueness and richness of biological diversity of Asia and Australia and also the transitional zone of the two continents is present in Indonesia. This is supported by the geological history and topology of Indonesia which is on the biodiversity's path of the Asian continent (Sumatra, Java, Kalimantan) and Australia (Papua) and in the transitional zone of the Wallace (Sulawesi, Maluku and Nusa Tenggara Islands). More than 75% of Indonesia's area is 81,000 km of shoreline marine; it is the second largest after Canada. This marine biodiversity is considered under explored and not fully studied (Anonymous, 2003; de Voogd,

2005). Therefore, nowadays Indonesia's marine biodiversity has become a target of world and domestic bio discovery, especially for marine natural products chemistry research.

World marine natural products chemistry research, in more than 20 years, has resulted many novel compounds, and some of them have been in the preclinical test for further commercialization, while some others are already commercialized (Faulkner, 2000). More than 2,700 research papers concerning sponges, the most secondary metabolite-rich compounds among marine organism, have been published up to year 2000 (Fusatani, 2000). There are approximately 850 species of sponge are believed to be present in Indonesia (de Voogd & van Soest, 2002), and up to 2007, at least 77 new compounds from 14 sponges and 19 new compounds from non-sponge organisms (soft coral, sea pen, octocoral and ascidians) with pharmacological potential. This review will cover natural products chemistry research using Indonesia's biota and trying to dig its pharmacological potential of Indonesia in order to supply Indonesia and ASEAN's pharmaceutical needs.

2. RESEARCH METHODS

This study used a kind of literature survey methods. It's examined the technical literature back to the earliest dates available on the topic of Mari culture and pharmacological potential of Indonesia's marine biodiversity. The specific terms searched were "Mari culture," "Indonesia marine biodiversity," and "biopharmaceutical." The data included:

- American Association of Pharmaceutical Scientist (AAPS)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- OMICS Publishing Group: Journal of Aquaculture Research
- Academic Journals

3. LITERATURE SURVEY RESULTS

MARINE BIODIVERSITY - Marine natural product research activities have been started by Indonesian researchers in 1990. However, due to some limitations in research resources, the progress is not significant especially in the form of international scientific papers, patent and commercial products. Mostly, bio discovery research activities done in Indonesia is superficial (*i.e.* preliminary screening towards various biological activities), and more depth activities are usually done in foreign country laboratories. Therefore, the products of invention of advance step such as structure of novel compounds, including patent of their product and process are usually under the properties of foreign- researchers. World marine natural products chemistry research, in more than 20 years, has resulted many novel compounds, and some of them have been in the preclinical test for further commercialization, while some others are already commercialized (Faulkner, 2000). More than 2,700 research papers concerning sponges, the most secondary metabolite-rich compounds among marine organism, have been published up to year 2000 (Fusatani, 2000). There are approximately 850 species of sponge are believed to be present in Indonesia (de Voogd & van Soest, 2002), and up to 2007, at least 77 new compounds from 14 sponges and 19 new compounds from non-sponge organisms (soft coral, sea pen, octocoral and ascidians) with pharmacological potential that will be described below.

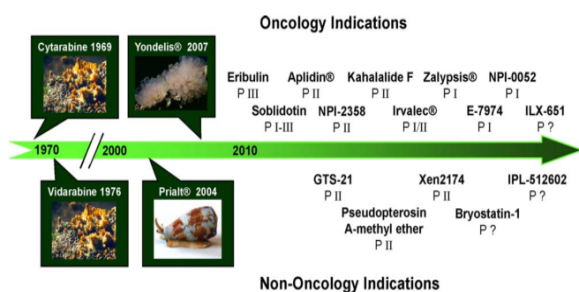
The distribution, ecological study as well as sponges bioactivity (based on its brine shrimp, *Artemia salina*, lethality assay) of Spermonde archipelago, Sulawesi were studied by de Voogd (2005). From the study, nine (9) sponges were considered potential to be developed. The sponge *Acanthodendrilla* sp. collected from Badi Island, Makasar, was investigated by William *et al.* (2004), identifying meroterpenoid MAPKAP (MK2) inhibitor. Mapkap kinase-2 is the compound that represents a potential therapeutic agent to treat inflammatory diseases. From the sponge *Stylissa carteri*, harvested from the waters in the same area, new alkaloids latonduines A and B were isolated by Linington *et al.* (2003), while two (2) new bromopyrrole alkaloids, *i.e.* debromostevensine and debromohymenin were isolated from the same sponge species collected from Ambon and Sulawesi waters (Eder *et al.*, 1999). Boneratamides A-C, new sesquiterpenoids, were isolated from sponge *Axinyssa aphysinoides* from the same surrounding Makasar waters (Williams *et al.* 2004), while a new acyclic diketotriterpenoid has been isolated from *Hyrtilis erectus* sponges, from the inner reef of Ujung Pandang. This new compound was biologically in-active, however, the crude extract of the sponge had significant antimutagenic activity (Williams *et al.*, 1999). Chemical study of the sponge *Leucetta chagosensis* from South Sulawesi waters found five (5) new imidazole alkaloids, namely naamine F, naamine G, kealiinine A., kealiinine B and kealiinine C (Hassan *et al.*, 2004). Naamine G showed antifungal activity against *Cladosporium herbarum* and mild cytotoxicity against mouse lymphoma and human cervical carcinoma (*HeLa*) cell lines. Crude extract of *Phyllospongia* sp. From Makasar's surrounding waters showed cytotoxicity, and seven (7) new scalarane class sesterterpenes have been isolated. All scalaranes isolated exhibited 30-95% inhibition of KB cells at a concentration of 10 µg/mL (Roy *et al.*, 2002). From sponge *Theonella swinhoei*,

harvested at Baranglombo Island, barangamide A, a cyclic undecapeptide possessing three N-methylated amino acids, and three β-alanines, have been isolated (Roy *et al.*, 1999). Further investigation on that sponge revealed that three (3) new cyclic peptides, barangamide B, C and D have been isolated along with four (4) new depsipeptides. Immunomodulatory test of these compounds showed that barangamide A exhibited no immunosuppressive activity up to concentration of 100 µg/mL, while all theonella-peptolides showed mild activity (Roy *et al.*, 2000). Study on sponge *Ianthella basta* from Manado Bay resulted in two (2) more bastadins, *i.e.* bastadin 16 and bastadin 17. Bastadin compounds are well known as predominantly macrocyclic sponge metabolite compounds (Park *et al.*, 1994). Bobzin *et al.* (2000) used dereplication techniques to identify aaptamine from the sponge *Aaptos* sp. which was harvested from Manado, northern Sulawesi, while Park *et al.* (1995) studied sponge *Luffariella* sp. from the same waters and isolated three (3) metabolites, *i.e.* aaptamine, germacrene alcohol and hexacyclic terpene. The metabolites showed *in vitro* activity against the KB cancer cell line. From the North Sulawesi sponge *Theonella cf. swinhoei*, bitungolides A-F have been isolated. The bitungolides were claimed as a new class of *Theonella* metabolites that are capable of inhibiting dual-specificity phosphatase VHR (Sirirath *et al.*, 2002).

In 1995, an unsymmetrical manzamine dimer called kauluamine, was isolated from sponge *Prianos* sp. harvested from Manado Bay (Ohtani *et al.*, 1995), while Makaluvamine G was isolated from the sponge *Histodermella* sp. The compound exhibited significant *in vitro* cytotoxicity to several tumor cell lines and moderate inhibition of topoisomerase I, DNA, RNA and protein synthesis (Carney *et al.*, 1993). From West Sumatra waters, four (4) new polybrominated diphenyl ether congeners along with 3 known derivatives have been isolated from sponge of *Dysidea herbacea* Keller (Handayani *et al.*, 1997). The new polybrominated compounds were active against a brine shrimp, and all the compounds isolated were positive against gram positive bacteria *Bacillus subtilis* and the phytopathogenic fungus *C. cucumerinum*. A sponge *Acanthodendrilla* sp. From Kundingarengke Island was investigated by Elkhayat *et al.* (2004), and 5 new luffariellolide-related sesterterpenes namely acantholides A-E, in addition to known luffariellolide and its 25-O-methyl and 25O-ethyl derivatives, have been isolated. The luffariellolide, its 25-O-methyl derivative and acantholide E exhibited cytotoxic activity against the mouse lymphoma L5187Y cell line. Acantholide B, luffariellolide and its 25-O-methyl derivative were active against *Escherichia coli*, *Candida albicans* and the pathogenic fungus *Cladosporium herbarum*. Twelve new sesterterpenes, honulactones A-L have been isolated from a lipophilic extract of the sponge *Stresichordaia aliena*, family Thorectidae, and further investigation led to the isolation of 6 new compounds of 20, 24-bishomoscalaran sesterterpenes, namely honu'enone, phyllofolactones H-K and phyllofenone C. The sponge was harvested from Turtle Bay, Sangkalli, Eastern Indonesia waters (Jimenez *et al.*, 2000).

Marine sponges harvested from waters surrounding Jakarta showed antimicrobial activity as well as cytotoxicity. The compounds isolated from the sponge *Xestospongia* were 4 novel alkaloids of the aaptamine class as well as known aaptamine, iso-aaptamine, demethyl (oxy) aaptamine and its dymethylketal (Calcul *et al.*, 2003). Their antimicrobial activity towards *S. aureus* (gram +), *E. coli* and *V. angillarum* (gram -), and the fungus *C. tropicalis* as well as cytotoxicity against human buccal carcinoma KB was investigated. The results showed aaptamine 1 and iso-aaptamine 2 exhibited antifungal activity, while significant cytotoxicity against KB cells was detected in aaptamine 1, iso-aaptamine 2 and demethyl (oxy) aaptamine 3. Bisdemethylaaptamine, a proposed biosynthetic precursor of aaptamine and bisdemethylaaptamine-9-O-sulfate, has been isolated from the sponge *Aaptos* sp. from near Bunaken Island, Manado. This was the first report of a sulfated aaptamine of bisdemethylaaptamine-9-O-sulfate (Herlt *et al.*, 2004). Meanwhile, the reddish brown, branching sponge *Echinochalina* sp. collected from Derawan Island, contained upenamide. This compound was a new class of macrocyclic marine alkaloid having both spirooxaquinolizidinone and hemiaminal ring systems (Jimenez *et al.*, 2000). Marine red alga (*Rhodophyta*) *Ceratodictyon spongiosum* and its symbiotic sponge *Sigmatocia symbiotica* harvested from Biaro Island have been investigated for their chemical substances. Two isomers of a new and bioactive thiazole-containing cyclic heptapeptide, namely cis,cisceratospongamide and trans, transceratospongamide have been isolated (Tan *et al.*, 2000). The last compound was capable of inhibiting the expression of a human-sPLA2 promoter-based reporter by 90%, while the first one did not show activity.

MARINE NATURAL PRODUCTS – Marine Natural Products (MNPs) offer an abundant source of pharmacologically active agents with great chemical diversity and complexity, and the potential to produce valuable therapeutic entities. The realization of this potential through the recent approval of two MNP therapeutics has been



taken many decades. The potential of marine natural products has captivated many researchers over the years. Inspired by the vastness of our oceans, and an almost

Fig. 1. Clinical development timeline for MNPs. After isolation in the 1950s and approval in 1969 (Ara-C, cytarabine) and 1976 (Ara-A, vidarabine), these MNP derivatives have been the only MNPs in clinical use. In 2004 with the approval of ziconotide and in 2007 of trabectedin, the promise of more MNPs as therapeutics appears to be imminent.

incomprehensible level of biodiversity in the marine environment, researchers have enthusiastically pursued the pharmacological potential of secondary metabolites from marine organisms. This is reflected in the numerous reviews on this subject matter in the past ten years (705 PubMed references for marine pharmacology as of January 2009) and that currently there are some 13 MNPs in some Phase of clinical development (<http://marinepharmacology.midwestern.edu/>), and more on their way. It has been almost five decades since the isolation of spongothymidine and spongouridine from the marine sponge *Tethya crypta* by Bergman (1957) that eventually led to the development of Ara-C (cytarabine, an antileukemia agent) and Ara-A (vidarabine, an antiviral agent), agents which received FDA approval in 1969 and 1976, respectively. Since the approval of Ara-C and Ara-A as therapeutics, it was not until 2004 that the next MNP would be approved, ziconotide (Prialt), for the treatment of severe chronic pain (Klotz, 2006). This was soon followed by the orphan drug status granted to trabectedin (Yondelis) for the treatment of soft tissue sarcomas and ovarian cancer, and its registration in 2007 in the EU for the treatment of soft tissue sarcoma (Schoffski *et al.*, 2008). However, the approval of so few marine natural products has come after many years of research primarily by the academic community and sporadic involvement of major pharmaceutical companies (Fig. 1).

These few approvals have not been due to a lack of discovery of novel marine natural products. Faulkner (2000), Blunt *et al.* (2008), and Mayer (2008) have provided comprehensive reviews of the total number of marine natural products discovered (D.J.F. and J.W.B.), and those with significant preclinical and clinical pharmacological activity (A.M.S.M.) for the years 1998–2006 (Table 1).

4. DISCUSSION

Table 1
Summary of MNPs identified and characterized between 1998 and 2006.

Year ^a	Chemistry and synthesis of marine natural products ^b	Preclinical and clinical marine anticancer pharmacology ^c	Preclinical and clinical marine pharmacology ^d
2006	779 [10]	136 [18]	183 [25]
2005	812 [9]		
2004	716 [14]	150 [17]	166 [23]
2003	656 [13]		
2002	677 [12]	97 [16]	106 [21]
2001	683 [11]		
2000	869 [8]	143 [15]	78 [20]
1999	881 [7]	31 [22]	66 [19]
1998	841 [6]	35 [24]	67 [26]
Total	6,914	592	666

^a Year of publication of articles reporting new marine natural products and/or preclinical and clinical pharmacology, and included in the corresponding annual review.

^b Number of novel marine natural products included in the respective annual review.

^c Number of marine natural products for which novel preclinical and clinical antitumor and cytotoxic pharmacology was included in the corresponding annual review.

^d Number of marine natural products for which novel preclinical and clinical pharmacology was included in the annual review. Marine compounds demonstrated anthelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; also affected the cardiovascular, immune and nervous systems, and presented several other miscellaneous mechanisms of action.

pharmaceutical sector are mostly discovered by foreign researchers. It means that, in our perspectives, if Indonesian researchers could cooperate and share ideas with them, Indonesia can get abundant of knowledge or ideas shared by many researchers around the world which is good as a basis to apply that practically. In addition, we also suggest to do some collaboration between the researchers and the stakeholders (e.g. the government, businessman or investor) in order to maximise Indonesia's marine biodiversity to their fullest economically and pharmacologically potential and to the real applications. Local cosmetics and traditional medicine industries have been using some marine organisms and plants extracts along with terrestrial plants. Those extracts, especially for an organism having

4.1 The Need of Bio discovery Research

Based on the review above, there are many economic and pharmacological advantages from Indonesian marine biodiversity that could be reached for Indonesia itself. However, there is still less research that has been conducted by Indonesian researcher to make it becoming real. The expensive sources and high risk under the sea are the reasons of why researchers don't take enough attention about these things. From those reasons, we suggest to the new government to allocate effectively higher budgeting on research projects in order to support researchers in doing research, not only in pharmaceutical field but also in every fields that could be the most strategic and competitive fields to be developed in Indonesia. Beside that, strengthening international cooperation is also an important thing to be considered. Looking to the results above, many bioactive compounds that are possible to use in

resistant cell walls, could be isolated by adding nanomaterials, which may be metallic nanofibers such as silver nanofibers. In Indonesian itself participation of local industries in a bio discovery-terrestrial plant has been initiated; however, their role in marine bio discovery is still very limited.

4.2 Mari culture Prospect in Indonesia

Indonesia is a maritime country which has abundant marine organisms. Nevertheless, this richness is not optimized yet. By this review we know that Indonesia still have a huge potential to optimize its marine biodiversity to gain economic advantages especially in pharmaceutical market. By doing mari culture, we could possibly maximize the use of total indicative potential area of national marine culture; we can nurture and cultivate the national marine organisms so the scarcity of marine organisms can be prevented as well.

5. CONCLUSIONS

In facing ASEAN Free Trade Area (AFTA), Indonesia has to strengthen all sectors to ensure if Indonesia will be placed in a good position in ASEAN without exception in pharmaceutical market sector. By its abundant resources of biodiversity, Indonesia has an opportunity to develop marine bio discovery program, biotechnology industry, and pharmaceutical industry for their people's prosperity. In order to ensure sustainability of bio discovery and Mari culture activities, we need the government support and encouragement to research institutions and biotechnological industries. This is include the developing of regulation on the access and also establishing biodiversity become an efficient and sustainable collection , introducing benefit sharing, providing support to the research centre and stimulating bio discovery research by improving research resources. These actions are really needed; otherwise the blessing of marine mega biodiversity the foreign prosperity will be lost.

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