

# Marine Natural Products: Prospects and Impacts on the Sustainable Development in Indonesia

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**Abstract**— Indonesia is worldwide recognized as being the richest in the world in term of diversity and number of marine organisms. These resources are massive supplies for food and medicine. A large variety of biologically active compounds with great biomedical interest such as anticancer, antibiotic, antioxidant, anti-AIDS, anti-TBC and anti-Alzheimer have recently been discovered from Indonesian marine invertebrates including microorganisms associated with them. However, drug development from the sea is often hampered by the difficulty of obtaining sufficient supply. In the other hand, long term exploitation in coastal and coastal and marine resources has caused severe environmental degradation. Hence, maintaining a sustainable capacity for the ecosystem is an urgency need. Integrating efforts on sustainable utilization of marine natural products, diversity conservation and economic development as well as strengthening relationship among government, public and stakeholders into one program could give social and economical benefits to the local society and Indonesia in general.

**Index Term**— Bioprospecting, Marine Natural Products, Sustainable development

## I. INTRODUCTION

Oceans cover more than 70% of the Earth, and appear to host 32 out of the discovered 34 phyla on Earth. A diversity of species per area unit is as high as 1000 species per square meter in the Indo-Pacific Ocean [1], and the highest species diversity occurs in coral reef ecosystems [2]. It therefore is not surprising that oceans are considered as vast untapped reservoirs of highly diverse and unique natural products. So far over 14.000 new biologically active compounds have been identified from marine sources. At least 300 patents have been issued on marine natural products [3], and more than 37 patents from the deep sea products were registered in the USA and Europe [4].

The majority of novel compounds have been secondary metabolites from soft-bodied invertebrates living in coral reefs

[3]. Among marine invertebrates, sponges belong to the richest sources of pharmaceutically active natural compounds.

Since the discovery of antiviral and antileukaemic nucleosides from the sponge *Cryptothelia crypta* by Bergmann and Feeney in the 1950's, thousands of sponge-derived bioactive compounds have been discovered, increasing the aura of sponges as high potential sources of new medicines [5]. Today, a new generation of pharmaceuticals derived from marine sponges are set to enter the market [3].

The global sales of marine natural products in 2002, including anti-cancer compounds, antibiotics and antivirals, were estimated at about US\$2.4 billion [6]. Annual profits of a drug based on a marine sponge-derived compound to treat herpes, for instance, account for US\$ 50 million to 100 million [1]. For such reason, there is an emerging interest among scientists and biotech companies in the research and development of new medicines from the sea, especially from marine invertebrates in the coral reef ecosystems. This interest has been strongly endorsed by the fact that the human genome is mostly sequenced now, which opens exiting opportunities of finding new potential drug targets. By analysis of the genes content in human genome to get insight on the function-structure of the encoded proteins, a large number of possible drug targets have been found which outgrow the number of existing pharmaceutically valuable compounds [7].

Indonesia as the world's largest archipelagic country with 17.508 islands and 81,000 km of coastline is worldwide recognized as being the richest in the world in term of diversity of marine organisms. Indonesian coral reefs in particular have the highest biodiversity in the world, forming the centre of high diversity of marine organisms [2]. This extraordinary biodiversity offers big opportunities and challenges for discovery of new genes, enzymes, secondary metabolites which might be very useful from both scientific and biomedical perspectives. However there is an increasing concern that the coral reef's condition in Indonesia is

currently under serious threat, mainly due to over-exploitative fishing methods (e.g. the use of toxic chemicals and dynamite coral mining practices, mangrove removal, and sediment accumulation derived from forest soils degraded by fires. Based on the information provided by the Indonesian Research and Development Centre for Oceanology at 414 stations within 49 locations, only about 6 % of the reefs are in excellent condition, while the rest are in various degrees of degradation, and the poor condition covers about 40 % [2]. This coral reef degradation not only reduces significantly the opportunities of gaining economic benefits from the exploration of marine natural products, but also can lead to long-term economic hardship for many rural peoples who are mostly dependent on the reef fisheries for their survival and income needs [8].

Recently drug discovery and development program based on the sustainable use of marine biodiversity have attracted much attention, because many scientists believe that its integration with recent advances in Biotechnology not only promises economic benefits but also promotes the protection and conservation of marine biodiversity. Some biotechnological innovations has enabled to generate ecologically and environmentally sound approaches, which contribute greatly to the sustainable use of marine biodiversity. This emerging multidiscipline is especially interesting to be developed in Indonesia as a tropical country with highly diverse marine resources. Therefore here we will deal with developing a concept about how drug discovery based on marine natural products can be implemented to promote the sustainable use, protection and conservation of marine biodiversity as well as to secure economic benefits to Indonesia.

## II. NATURAL PRODUCTS FROM INDONESIAN MARINE ORGANISMS

Marine natural product has attracted attention of chemists and biologists for the past five decades. This is due to the fact that natural products from the sea have shown very interesting molecular structure and promising biological activities. Marine natural products are mostly derived from marine invertebrates such as sponges, soft corals, ascidians, gorgonians, sea pens, algae and fungi.

### A. Sponges

Sponges are aquatic animal of the phylum *Porifera*. They are primitive, sessile, mostly marine, water dwelling filter feeders that pump water through their bodies to filter out particles of food matter. Sponges are divided into classes based on the type of spicules in their skeleton. The three classes of sponges are bony (*Calcarea*), glass (*Hexactenellida*) and spongin (*Demospongiae*). Natural products from Indonesian sponges are mostly derived from spongin (*Demospongiae*) for example *Haliclona sp.*, *Xestospongia sp.*, *Theonella sp.* and *Hyrtios sp.* Table 1 summarizes novel compounds isolated from Indonesian sponges and their structures are shown in Fig.1.

Research in Indonesian sponge was started in late 1980's by Corney *et.al.*, who discovered two new macrolides from *Hyatella sp.* namely laulimalide and isolaulimalide. Both compounds exhibited cytotoxicity against KB cell line ( $IC_{50}$ =15 ng/ml). Furthermore, laulimalide also demonstrated a high level of potency against the multidrug resistant cell line SKVLB-1 ( $IC_{50}$ ) 1.2  $\mu$ M). In contrast, isolaulimalide is significantly less potent against the KB cell line ( $IC_{50}$  > 200 nM) as well as the SKVLB-1 line ( $IC_{50}$ ) 1.6 mM). These results indicate that the epoxide moiety of laulimalide is critical for enhanced antitumor activities. Recent studies also reported that laulimalide act as a microtubule-stabilizing agent and inhibited the *P*-glycoprotein that is responsible for multiple-drug resistance in tumor cells. It also has been shown that laulimalide is as much as 100-fold more potent than Taxol in multi-drug-resistant cell lines. Thus, laulimalide represents a new class of microtubule-stabilizing agents with significant clinical potential [9].

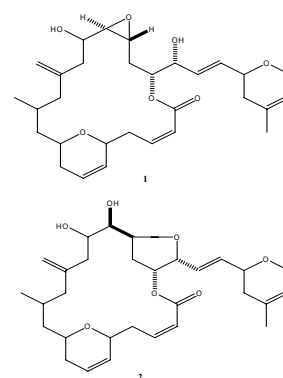


Fig.1. Laulimalide (1) and Isolaulimalide (2)

In 1993, Carney, *et.al.* isolated makaluvamine G, a pyrrolloquinoline alkaloid from *Histodermella sp.* which also displayed significant in vitro cytotoxicity to several tumor cell lines and was a moderate inhibitor of topoisomerase-I, DNA, RNA, and protein synthesis [10]. In the same year, Ichiba *et.al.* isolated two new bromo-substituted polyunsaturated  $C_{16}$  fatty acids from an Indonesian sponge, *Oceanapia sp.* [11].

Two antitumor compounds, manadic acid A-B [12] and elenic acid [13] were found afterward from *Plakortis sp.* and *Plakinastrella sp.* respectively. Manadic acid A was found to be moderately active as antitumor agent and immunomodulator, while manadic acid B only displayed activity as antitumor against various tumor cell lines. Both compounds, however, were inactive as anti-HIV. Elenic acid performed cytotoxicity with  $IC_{50}$  of 5  $\mu$ g/mL in P-388, A-549 and MEL-28 by inhibiting topoisomerase II, which is considered to be an indicator enzyme in the treatment of lung cancer at 0.1  $\mu$ g/mL. During 1994-2000, more novel compounds were reported, however most of them did not own any interesting pharmacological activity. Park *et.al.* [14-15] investigated a series of bastadins, tyrosine derivatives from *Ianthella basta*. Kumusine from *Theonella sp.*[16], kauluamine from *Prianos sp.* [17], waiakemikeamide, a peptide from *Ircinia dendroides* [18], clathryimine A from

*Clathria basilana* [19], laulimalide, a macrolide from *Hyattella* sp. [20], noelaquinone from *Xestospongia* sp. [21], diketotriterpenoids from *Hyrtilos erectus* [22] and barangamide A-C [23]-[24], a series of peptide from *Theonella swinhoei* were also reported. Only one paper demonstrated bioactive novel compounds from *Axinella carteri* [25]. Six novel unusual alkaloids were isolated, including the new brominated guanidine derivative, 3-hymenialdisine. Hymenialdisine and debromo hymenialdisine were found to exhibit insecticidal activities toward neonate larvae of the polyphagous pest insect *Spodoptera littoralis* (LD<sub>50</sub> 80 ppm and 125 ppm, respectively). Debromohymenialdisine, hymenialdisine and 3-bromohymenialdisine also displayed cytotoxicity against mouse lymphoma cell, while the remaining alkaloids were inactive.

Starting from year 2000, significant development of natural product research from Indonesian marine organisms was increasing. From marine sponge, *Strepsichordaia aliena*, Jimenez and co-workers discovered honulactones A-L, which showed cytotoxicity against P-388, A-549 HT-29, and MEL-28 (IC<sub>50</sub> 1 µg/mL) [26]. Whilst Aoki *et al.* obtained a series of novel polyacetylenes from *Haliclona* sp. known as lembehynes A-C exhibiting neuritogenic activity in pheochromocytoma PC12 and neuroblastoma Neuro 2A cells at 2 and 0.1 µg/mL [27]-[28]. Further research revealed that the carbon chain length and hydroxyl group at C-3 in lembehynes are important for its activity, while the unsaturated bonds are not.

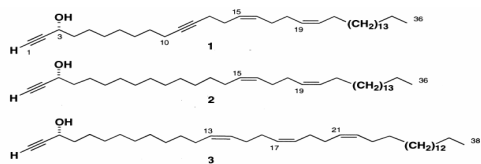


Fig.2. Lembehyne A (1); Lembehyne B (2); Lembehyne C (3)

Labuanine A, a new pyridoacridine alkaloid was also obtained from *Biemna fortis*, inducing neuronal differentiation in a neuroblastoma cell line [29]. A novel modulator of multidrug assistance (MDR) in tumor cells, kendarimide A from *Haliclona* sp. was reported in the following year [30]. Another sequence of anti-angiogenic steroidal alkaloids, cortistatins J-L was isolated from *Corticium simplex*, but only cortistatin J showed cytostatic anti proliferative activity against human umbilical vein endothelial cells (HUVECs) at 8 nM [31]. The differentiation of K562 chronic myelogenous leukemia (CML) cells by smenospongine from *Dactylospongia elegans* was also examined [32].

Six studies contributed to the search for novel antimicrobial natural products were performed throughout 2003-2007. Three series of terpenoids were isolated from *Haliclona* sp., *Melophlus sarassinorum* and *Acanthodendrilla* sp. labeled as halicotriol A-B, sarasinosides J-M and acantholides A-E correspondingly [33]-[35]. Calcul *et al.* investigated novel alkaloids of aaptamine class from marine sponge of the genus

*Xestospongia* [36]. Their antimicrobial activity was tested towards gram positive (*S. aureus*) and gram negative (*E. coli* and *V. anguillarum*) bacterial strains and a fungus (*C. tropicalis*). Hanif *et al.* also reported novel polybrominated diphenyl ethers possessing antimicrobial activity against *Bacillus subtilis* and moderate/weak cytotoxicity against NBT-T2 rat bladder epithelial cells from *Lamellodysidea herbacea*, suggested that the presence of two phenolic hydroxyl groups and bromines at C-2 and/or C-5 is important for the exhibition of antibacterial activity [37].

Rao's work in 2003-2006 has contributed eighteen new manzamines alkaloids along with two beta carbolines and five nucleosides isolated from *Acanthostrongylophora* sp. potential as tropical diseases treatments (malaria and leishmania) as well as TBC and antimicrobial agent. All the reported oxamanzamines, however, were inactive against *M. tuberculosis*, *P. falciparum*, and *L. donovani*. SAR studies indicated that reduction of the C-32 and C-33 olefin and oxidation of C-31 also significantly reduces the antimalarial activity for the manzamine alkaloids in vivo. The significant differences in biological activities of manzamine A, manzamine E, and their corresponding 12,34-*oxa*-derivatives indicate that the C-12 hydroxy, C-34 methine, or the conformation of the lower aliphatic rings plays a key role in the antimalarial and leishmanicidal activity and provides valuable insight into the structural moieties required for activity against the malaria and leishmania parasites. The difference in the antimalarial and antileishmanial activities of manzamines A and J indicates that the bond between N-27 and C-34 may be important for the antimalarial and leishmania activity. Comparison of the *M. tuberculosis* and antimalarial activities of manzamine E and its hydroxyl derivatives indicates that the hydroxyl functionality and its position on the  $\beta$ -carboline moiety may play a role in biological activity. The significant leishmanicidal activity of ircinal A, IC<sub>50</sub> 0.9 µg/mL and IC<sub>90</sub> 1.7 µg/mL indicates that the  $\beta$ -carboline moiety is not essential for activity against the leishmania parasite in vitro, which is significantly different from the malaria structure-activity relationship [38]-[40]. Furthermore, Hamann *et al.* investigated that manzamine A is effective in increasing tau hyperphosphorylation in human neuroblastoma cell lines and inhibiting glycogen synthase kinase-3 (GSK-3), thus it can be designed as potential therapeutic agents for Alzheimer's disease [41].

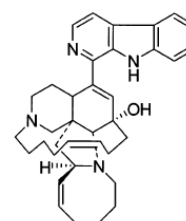


Fig.3. Manzamine A

Manadomanzamines A, B as well as hydroxymanzamine A also exhibited strong activity against *Mycobacterium*

*tuberculosis* (Mtb) with MIC values of 1.9, 1.5 and 0.91  $\mu\text{g/mL}$ , respectively. The first two also exhibit activities against human immunodeficiency virus (HIV-1) and AIDS opportunistic fungal infections [42].

Several other compounds possessing antitumor were also discovered and identified as bitungolides from *Theonella swinhoei* [43], puupehenone from *Hyrtilios sp.* [44], naamines and naamidines from *Leucatta chagosensis* [45]-[46], plakorstatins from *Plakortis nigra* [47], and coelidiol and coeloic acid from *Coelocarteria cfr. singaporensis* [48].

Rashid *et.al.* reported the discovery of microspinosamide in 2001 from *Sidonops microspinosa*, effective in inhibiting the cytopathic effect of HIV-1 infection in an XTT-based in vitro assay with an  $\text{EC}_{50}$  of 0.2  $\mu\text{g/mL}$  [49]. Whilst Suna *et.al.* isolated a pentacyclic guanidine alkaloid, crambescidin 800 from *Monanchora unguiculata*, which protects a mouse hippocampal cell line against glutamate-induced oxidative stress [50]. More papers reported the investigation of novel compounds afterward from various species of sponges but containing no pharmacological activities [51]-[62].

### B. Soft corals

Soft corals, along with hard corals, are in the Phylum Cnidaria, members of the order Alcyonacea having in common a very simple body plan and polyp structure. Corals can grow to over 2 feet across in the wild, and are found in a variety of colors. Soft corals are found mainly in tropical waters around the world in varying environments ranging from coral reefs to inter-coastal channels at depths up to 150 feet. Soft corals help maintain the health and balance of reef ecosystems and provide protection to numerous animals. In the other hand, many soft corals also exude mucus with traces of chemicals that repel other organisms such as sponges and algae, which might otherwise growth too close or over the top of the soft coral.

Unlike sponges, research in Indonesian soft corals is much less. From 1997-2002, only three studies reported the findings of novel compounds from Indonesian soft corals. Handayani *et.al.* investigated *Nephtea chabrolii* to afford two novel sesquiterpenes, hydroxycolorenone and methoxycolorenone [63]. This is the first report of the occurrence of such terrestrial liverwort metabolites in marine soft corals. Hydroxycolorenone exhibited insecticidal activity towards neonate larvae of the polyphagous pest insect *Spodoptera littoralis*, with an  $\text{EC}_{50}$  of 8.8 ppm and a  $\text{LC}_{50}$  of 453 ppm.

A secosterol with a gorgosterol side chain and an unusual oxygenation pattern on the A and B rings was discovered by Morris *et.al.* from *Lobophytum sp.* and reported to have antitumor and antileukemia activity against human ovarian tumor and human leukemia cell lines [64]. In 2002, Anta *et.al.* also identified a series of xeniolides, diterpenoids from *Xenia sp.* No activities were reported [65].

### C. Ascidiaceans

Ascidiacea (commonly known as the ascidians or sea squirts) is a class in the Tunicata subphylum of sac-like marine filter feeders. While members of the Thaliacea and

Larvacea swim freely like plankton, sea squirts are sessile animals: they remain firmly attached to substratum such as rocks and shells. There are 2,300 species of ascidians and three main types: solitary ascidians, social ascidians that form clumped communities by attaching at their bases and compound ascidians that consist of many small individuals (each individual is called a zooid) forming colonies up to several meters in diameter.

*Lissoclinum cf. badium* and *Polycarpa aurata* were reported to contain lissoclibadins [66] and polycarpaurines [67], correspondingly. All compounds were found to inhibit colony formation of Chinese hamster V79 cells. Lissoclibadins also showed weak antimicrobial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Saccharomyces cerevisiae*. From the same genus to *Lissoclinum cf. badium*, *Lissoclinum patella* also producing *Lissoclinamide* 9-10, peptides with no pharmacological activity [68].

Two other alkaloids were discovered by Copp from *Eusyntyla latericius* and Smith *et.al.* from *Didemnum sp.* and identified as styelamines [69] and plakinidine D [70], respectively. Styelamines are a series of pyridioacridine alkaloid which typically consist of tetra- or pentacycles and possess a functionalized alkylamine side chain. Plakinidine D is classified as pyrrolloacridine that closely related to plakinidines A-C, previously isolated from the sponge *Plakortis sp.* Another unique but inactive compound, 1,3,0-7-trimethylisoxanthopterin, was also reported by Van Wagoner from *Eudistoma sp.* [71].

### D. Gorgonians

These large coral colonies are easy to recognize because of their fan shape. A flexible, horny substance called *gorgonin* forms this coral's central skeleton, which supports all branches of the colony. Living tissues form a layer over the skeleton's entire surface. A gorgonian, also known as sea whip or sea fan, is an order of sessile colonial cnidarian found throughout the oceans of the world, especially in the tropics and subtropics. Gorgonians are classified in the phylum Cnidaria, class Anthozoa, alongside the orders Alcyonacea (soft corals) and Pennatulacea (sea pens). There are about 500 different species of gorgonians found in the oceans of the world, primarily in the shallow waters of the Atlantic near Florida, Bermuda, and the West Indies.

Gorgonians belonging to the genus *Junceella* (Gorgonacea) are known to produce highly oxidized diterpenoids of the briarane class (3,8-cyclized cembranoids). Garcia *et.al.* reported a series of junceollolides, possessing chloro substituents and epoxide groups from *Junceella fragilis* [72]. Other new diterpenoids, stecholide H and J, also discovered from *Briaerum sp.* [73]. However, both junceollolides and stecholides compounds were found to have no biological activities.

In the other hand, *Isis hippuris* is recognized as a rich source of cytotoxic polyoxygenated steroids. Thirteen novel steroids were isolated by Gonzales *et.al.* and reported to have cytotoxic activity [74]. Further investigation showed that the

steroids bearing a spiroketal ring are more active than those without this feature.

#### E. *Sea pens and algae (associated with marine sponges)*

The sea pens *Pennatulacea* is one of four orders of the *Octorallia* class, identified by the eight tentacles. There are 14 families within the order; they are thought to have a cosmopolitan distribution in tropical and temperate waters worldwide. Sea pens are grouped with the octocorals ("soft corals"), together with sea whips and sea feathers. Preferred habitat among sea pens is muddy substrate in sheltered fjords. They live on all depths from 15-20 meters and down. So far, only one paper is reported the finding of novel compound from Sea Pen, *Varetillum malayense*.

Fu *et al.* isolated malayenolides A-D, four new briarane diterpenes, which exhibit toxicity on brine shrimp lethality test (BSLT). The new diterpenes possess benzoate and senecioate substituents, both of which are rare among marine natural products [75].

Another marine organism which also considered as a potential source of bioactive novel compounds is algae. Marine algae are a large and diverse group of simple plant-like organisms, ranging from unicellular to multicellular forms. The largest and most complex marine forms are called seaweeds. They are considered "plant-like" because of their photosynthetic ability, and "simple" because they lack the distinct organs of higher plants such as leaves and vascular tissue. Many modern sources restrict the term *algae* to eukaryotic organisms. Some species of algae form symbiotic relationships with other organisms. In case of algae with symbiotic sponges, the algae supply photosynthesis (organic substances) to the sponge providing protection to the algal cells.

In 2000, Tan and co-workers discovered new bioactive cyclic heptapeptides, namely *cis,cis-* and *trans,* *trans-ceratospongamides* from the red algae *Ceratodryction spongiosum* with its associated sponge, *Sigmatocia symbiotica*. However, only *trans,* *trans-ceratospongamide* was found to exhibit potent inhibition of sPLA(2) expression in a cell-based model for antiinflammation (ED<sub>50</sub> 32 nM), whereas the *cis,cis* isomer is inactive. *Trans,* *trans-ceratospongamide* was also shown to inhibit the expression of a human-sPLA(2) promoter-based reporter by 90% [76].

#### F. *Fungi*

During 2000-2008, three studies on marine fungi were conducted. Fermentation of marine fungal species I96S215 was found to afford novel hexaketide metabolites, *iso-cladospolide B*; *seco-patulolide C* and 12-membered macrolides, *pandangolide 1* and *pandangolide 2* [77]. From the sponge associated marine fungi, *Aspergillus versicolor*, is reported to yield 6 new chromone derivatives namely *aspergione A-F* [78]. Another study also reported six new highly oxygenated angucyclinone polyketides, namely *panglimycins A-F*, isolated from the extract of *Streptomyces* strain ICBB8230 [79]. None of the compounds mentioned above exhibited potential bioactivity.

### III. POTENTIAL IMPACTS OF MARINE NATURAL PRODUCTS ON SUSTAINABLE DEVELOPMENT

#### A. *Drug discovery based on marine natural products*

Drug discovery and development based on marine natural products are multidisciplinary consisting of discovery process and development process. The discovery process involves bioprospecting as the initial step. Bioprospecting meant here is collection of samples of living resources (*e.g.* plants, animals and microbes) from a large range of areas for commercial purposes [4]. A key function of bioprospecting is to provide some of the thousands of compounds that have interesting structures or activities [80].

In the drug discovery process, thousands of extracts from the marine organisms collected during the bioprospecting expedition are prepared and subsequently tested for activities against various target infectious diseases or cancers. Usually only a small number ("hits") are registered for bioactivity. To develop a hit into a candidate of preclinical trials called "lead", the hit extract is purified first to find the active compound and then the structure is elucidated. It may need 50.000-100.000 active compounds to generate a single lead [3].

In the development process which is usually handled by the companies, a lead compound is subjected to a series of preclinical and clinical trials. To set a lead into such trials, there would normally be a need for an additional supply of sample material. In preclinical phase, at first efficacy and toxicity tests of the lead are established *in vivo* in animals. If this step is successful, the tests proceed with humans in clinical trials. Only one in about 50 preclinical leads will result in a marketable drug [3]. Both process takes approximately 15 years, with the research and clinical phases lasting up to 13 years and the administrative phase between two to three years [1]. The development of a new drug is expensive which spends cost of US\$900 million [3] or over a billion US dollars the cost of bringing a product from its conceptualization to the market [81].

#### B. *Benefit sharing issues*

As described above, the conversion of marine natural products into a clinically-used drug is complicated, lengthy and expensive. Therefore, the mechanism of fair benefit-sharing needs a proper negotiation between the pharmaceutical companies as the developers, the involved research institutions, and the biodiversity-controlling governmental agencies representing the source local communities. If benefit sharing agreements could not be achieved, we assume that the opportunities to develop the marine biodiversity which will bring tangible benefits to the source country as well as to the interested companies will be increasingly reduced.

Benefit-sharing issues arising from the use of genetic resources are in general fully addressed in the Convention on Biological Diversity (CBD). These issues are especially contained in the articles 15 to 21, which address: access to genetic resources, technology transfer, exchange of information, technical and scientific co-operation, handling of biotechnology and benefit distribution, financial resources, and the financial mechanism [1]. In principle this benefit

sharing should achieve a balance between the expectation of equitable benefits and the need for source countries to get the value of their natural resources [80]. The participating scientists within the involved institutions should also benefit from the use of genetic diversity by protecting their discoveries from claims and accusations of unethical research practices. There should be legal access framework agreements to secure that their research activities will not be exposed to the accusations [82].

However, many countries have developed appropriate mechanisms for reasonable benefit-sharing from accessing their genetic resources. The benefit-sharing mechanisms are usually developed based on understanding among the involved parties about the goals in the drug discovery and development program. It is important for the involved parties to understand that in the drug discovery process which is usually performed by the research institutions, the majority of the research results produces science with no immediate commercial goal. For such reason this process is considered as non-commercial research. Since the success rate at this process stage is exceedingly low, it seems difficult for the involved companies to make the financial benefits in the form of royalties to the source communities [80]. However during this discovery process, a number of non-monetary benefits to the source country or the local communities could be developed, including promotion of biodiversity conservation, eco-tourism, scientific infrastructure, technology transfer and education as described in the later section.

Nevertheless, when a compound is set to enter the drug development process, it should be considered as commercial research, because the research is focused on compounds with a higher chance of proceeding to the market. At this stage, the payments in the form of royalties should be properly negotiated between the developer and the governmental representatives from the source country or the local communities. An example of the mutual benefit-sharing is between Costa Rica's National Biodiversity Institute (INBio) and the biotech company, Merck & Co in 1991. Merck advanced INBio US\$ 1 million as well as training and infrastructure support for a National Park Fund. By 1999, Merck had invested over US\$ 3.5 million for a number of natural products extracts, and a half was allocated as future royalties for conservation purposes [7].

### *C. Promoting conservation of marine biodiversity*

The concept of non-monetary benefits (short-term benefits) to the source country can be developed during the drug discovery process. For example, the bioprospecting activities in the early stage of the process provide data on the identity of the collected marine organisms. In addition, environmental physical and chemical parameters are measured. All of these data are very useful for the governmental policy makers in the efforts for effective planning of protection and conservation managements. Furthermore, the availability of biodiversity information in the bioprospecting sites can attract much more attention for visitors or tourists, greatly increasing the ecotourism experience [80].

One of the best known approaches in linking between bioprospecting and biodiversity conservation is Yellowstone, a US National Park popularly recognized with its hot springs. The incentives associated with the research activities not only strengthen research but also contribute to the efforts of the sustainable conservation of the Park's resources. From the conservation aspect, Yellowstone obtains improved data about microbial distributions at the park from visiting researchers. Protection of these resources can be strengthened by directing scientists to thermal habitats with desired organisms while at the same time ensuring that the park's thermal resources are being protected [83].

Marine bioprospecting also can create incentives to protect biologically diverse and threatened marine ecosystems, including coral reefs and deep-sea habitats in Indonesia seas. A half of these incentives could be invested for providing educational opportunities of lifelong learning to the general public, including school students, families and other social organizations, aiming at introducing them with marine life and the importance of marine biodiversity conservation. This may involve interactive video and live approaches to attract them into the exciting marine biodiversity topics. This lifelong learning can be incorporated with marine trip programs to make them interacted directly with the nature. It is also very useful to allocate the incentive for a public library through providing various semi-popular books with full interesting pictures relating to marine life topics in order to advancing their understanding of the science behind the biodiversity. All these efforts are aiming at growing the carelessness of the public, especially the children as the biodiversity inheritance, to the marine environment as well as enhancing their awareness to participate in maintaining the quality of marine life.

### *D. Improving scientific capacity and education*

Other benefits derived from the drug discovery process may include the improvement of scientific capability of the researchers, training opportunities for undergraduate students, and improvement or even setting up of scientific infrastructure in the source country. By having research experience, young researchers have bigger opportunities to result peer-reviewed publications, to compete for further education and even to earn international/external funding. For example, through collaboration between Research Centre for Marine and Fisheries Product Processing and Biotechnology (RCMFPPB-Jakarta) and Australian Institute of Marine Sciences (AIMS-Townsville), some research staffs have gained scientific experiences and further education in Australia.

The lack of infrastructure capacity hampers the investment of the biodiversity-based research in Indonesia that could generate patentable pharmaceutical products. In this case it is necessary to make a proper agreement with the participating companies about building the necessary infrastructure capacity in the source country. The presence of the infrastructure will make feasible to carry out the drug discovery process in the source country. Whereas the drug development is done by the companies. A good example of a short-term benefit implementation through the infrastructure improvement is the biodiversity-based research collaboration between the

International Cooperative Biodiversity Groups (ICBG) and Panama. Through this collaboration, two laboratories were set up in Panama by using ICBG funds, and several existing laboratories were improved by providing the first nuclear magnetic resonance facility. The infrastructure investment provides new jobs without the use of the government funds [80].

#### E. Securing the sustainable economic benefits

Transformation of marine natural products into commercially available drugs requires a long time (approximately 15 years), and when a compound reaches patent protection and the transition to commercial research, final negotiation on benefit sharing should be made in the form of royalties. A good example for benefit sharing in the form of royalties was shown by a collaboration between the bioproduct developer, Diversa Corporation and the US National Park, Yellowstone. In this term, a heat tolerant enzyme from Yellowstone *Thermus aquaticus*, called *Taq* DNA polymerase, has been developed as the main key in the polymerase chain reaction (PCR) technology from the late 1980s. This enzyme-based technology has contributed greatly to the accelerated growth of the biotechnology industries and has generated revenues in excess of several hundred million dollars per year. Through the properly negotiated arrangement, Diversa Corporation (San Diego, California) has shared these revenues with Yellowstone [83].

Once financial sharing in the form of royalties (annual payments or per-sample fees) has made to the source country, it should reach the local communities where the medicine originally discovered from. A part of the royalties could be used to improve the economic growth of the local communities. The remaining could be invested in education of children and young peoples in order to prepare the coming generations who are capable to conserve and use of marine biodiversity in their homeland. This educational investment could be implemented by building a marine education institute based on the laboratories established previously. This research-based institute should open access to the potential students from the local communities and cover the whole or a part of their study financial needs. In order to maintain the flow of both short-term and long-term benefits, the experienced researchers in the institute should be able to earn international funding for their project plans and develop research collaborations with both biotech companies and other relevant institutions abroad.

### IV. OBSTACLES AND SOLUTIONS IN MARINE NATURAL PRODUCT INDUSTRIALIZATION

#### A. Material continuity

A serious obstacle to the ultimate development of most marine natural product (or marine bioproduct) currently under clinical trial or in preclinical evaluation is the problem of material supply. The metabolite often occurs in trace amounts in the organism tissue, and a steady source of supply from wild harvest cannot provide enough of the target compound for preclinical studies. In general, the natural abundance of the

source organisms will not support production based on wild harvest [84].

As describe above, marine bioprospecting generally occur in two stages. The first stage in the beginning of the drug discovery is called primary collection which covers small quantities of samples from a large number range of spesies. The second stage in the beginning of the drug development is called secondary collection which covers much larger quantities than in the primary collection [3]. If the quantities of a collected targeted organism reach the levels which endanger the survival of wild population, this collection stage is considered to be ecologically unsustainable and could give negative impact to the environmental balance.

Possible risks of ecological impact from the secondary collection may be minimized with a combination of self-regulation by industry and research-associated groups and active management by the local community. Industry self-regulation may involve i) development of environmentally sound protocols for sample collection, and ii) timely and precautionary assessments of economic and ecological viability [3]. These supply issues represent some of the most serious technical, economical and ecological challenges in the development of marine natural products. Therefore, generally applicable approaches that could overcome this supply problem are needed urgently.

Recent developments in Biotechnology have generated some approaches to counteract the supply problem, avoiding the secondary collection. In principle, there are a number of supply strategies as follows [84]-[87]:

1) Aquaculture/mariculture, bioreactor, and cell or tissue culture. Shallow water specimens may be transplanted and grown in sheltered waters or in artificial raceways but the successful culture of deep water specimens may require considerable research effort.

2) Chemical synthesis. This could be performed for relatively simple compounds. A terrestrial example is aspirin, in which the commercial product is synthesized rather than obtained from its natural product source. However, many bioactive marine natural products are extremely complex and require multi-step synthesis of heroic proportions. For these more complex molecules, it seems best to elucidate the mechanism of action and identify the pharmacophore so that simpler compound can be synthesized.

3) Microbial cultivation. Many pharmaceutically valuable marine invertebrates contain vast numbers of microorganisms that can occupy a substantial portion of the animals' wet weight. It has been suspected for a long time that such symbiotic microorganisms might be the actual producers of many natural products. If the compound producer is microorganisms, microbial cultivation becomes a good option to pursue. However this option is restricted by the fact that more than 99.8% of microbial diversity in most environments are unculturable [88].

4) Genetic Engineering. The ability to transfer genetic material from one bacterium to another, has opened up the exciting possibility of transferring segments of DNA that are responsible for the biosynthesis of secondary metabolites from

individual compound-producing microorganisms to *Escherichia coli* or other appropriate microbial hosts.

With recent advances in information technology, genetic engineering has been developed further into a new powerful approach called metagenomics. This approach has enabled rapid discovery of biosynthetic pathways from marine invertebrates and the associated uncultivable microbial consortium. Subsequent transfer of them into easily cultured bacteria allows the sustainable production of marine drugs. Its integration with rational protein design, popularly called combinatorial biosynthesis, even permits creating novel pharmaceutical compounds with largely predictable structures and truly unique pharmacological profiles [89]. It is clear here that the use of the advanced techniques in Biotechnology has permitted the sustainable use of marine biodiversity in the drug discovery program. The process of these approaches are feasible to be developed in Indonesia in collaboration with some relevant scientists abroad.

#### *B. Lack of multidisciplinary integration*

Exploration of marine natural products in the effort of drug discovery offers promising economic benefits. This will depend on a number of factors, including identification of new bioproducts, sustainable use of the product, optimization of production, and efficient product recovery. To achieve the sustainable exploration, it would require the integration and collaboration of multidisciplinary teams of oceanographers, biologists, chemists, and engineers [90]. In addition, the effort of bringing marine natural products to the market plays an important role. This needs an effective marketing strategy to compete in this globalization era. The failure in promoting those valuable products could give no economic impact to the source country.

#### *C. Overlapping of inter-institutional research*

So far there are no close collaboration and good coordination among the universities, research institutes and companies in the research on marine natural products in Indonesia. As a result, overlapping in the research focuses or repeating the same research stages often occurs. This not only wastes a lot of time but also costs much more funds. It needs dialogues to facilitate collaboration and to manage the research focuses among universities, research institutes and business partners. Patent or Intellectual Property Rights (IPR) can be one of tools to perform reliable collaboration, as well as common trusty among all parties. These collaborations are definitely essential to make a swift process of establishing and developing of research-based companies.

#### *D. Lack of governmental support and infrastructure*

Drug discovery and development require high costs and long time frames. Although the results of the processes promise the high returns, they entail the high risks [91]. In this case, the role of the government, i.e. Ministry of Health and Ministry of Marine Affairs and Fisheries to release national policy regulating this scheme is important. The long-term policy which is not dependent on the temporal succession of the governmental authorities is required to maintain the

industrialization flow of marine natural product. In addition collaboration of all stakeholders including research institutes/universities and business partners on industrialization of marine natural product could be speed up by the government. The involved parties should be able to make a link between marine natural products and the sustainability of marine resources and social economic development.

There are some steps in the drug discovery development processes that could be carried out in Indonesia based on the existing infrastructure and facilities. In principle this could follow the same pattern seen in the industrialized countries [80]. It will be as a shortcut for the company in the source countries, such as Indonesia. Furthermore infrastructure support could be acquired through international collaboration or partnership with the involved multinational companies, in which the fabrication is based in Indonesia. This could provide multiple effects to the local communities, such employment absorption or other economic activities. With this approach, technology transfer itself could develop vastly.

#### *E. Lack of the local people's involvement*

So far the participating companies gain many economic benefits from accessing the natural resources. On the other hand the local communities gained no significant benefits from the use of their genetic resources. To give benefits to the local people, bioprospecting could be properly managed well in order to be able to involve them actively. For instance, a reasonable proportion of royalties is used for the direct benefit to the people surrounding the collection area, such as education or capacity building, and employment. In addition, marine bioprospecting should provide an incentive for conservation. The samples taken during bioprospecting should be sustainable and accessible. For conservation rationale, it should not use endangered species as a medicine source.

### V. CONCLUSION AND RECOMMENDATION

Drug discovery program based on the R & D of marine natural products undoubtedly offers promising economic benefits to Indonesia with highly diverse marine resources. Recent breakthroughs in Biotechnology has enabled the implementation of this program in ecologically sustainable ways. This program can be developed in Indonesia through a close collaboration among the research institutions, the pharmaceutical companies, and biodiversity-controlling governmental agencies representing the source country. With properly negotiated benefit-sharing agreements, Indonesia could gain many benefits from the use of Indonesian genetic resources, including biodiversity conservation, eco-tourism, scientific infrastructure, technology transfer and education, and monetary royalties. To give significant economic impacts, we suggest that this benefit sharing concept should be initially performed in a small-scale, in this respect the regions where the 'owner' communities live. In this term, this could be used as a model at the national level, which could subsequently be applied in other parts of Indonesia with high marine

biodiversity. If this concept is developed in a larger scale, we are convinced that this can contribute significantly to the national economical sustainability.

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