AN EMERGING MARINE BIOTECHNOLOGY: MARINE DRUG DISCOVERY

Perkembangan Bioteknologi Kelautan: Upaya Menemukan Obat dari Laut

Nurrahmi Dewi Fajarningsih

Research and Development Center for Marine and Fisheries Product Processing and Biotechnology
Corresponding author: nrrahmi_dewi@yahoo.com. KS. Tubun Petamburan VI Jakarta Pusat 10260

ABSTRACT

Marine natural resources offer an opportunity to discover a novel chemical diversity with interesting pharmacologically active compounds to treat many diseases such as cancer, inflammation, bacterial and parasitic infections, and many other diseases. Marine drug discovery is a rising area in marine biotechnology. Several hits of marine-derived drug compounds were approved; two of them are Ziconotide and Trabectedin. In 2004, Ziconotide was approved as pain treatment drugs in the United States and Europe. Then, in 2007, Trabectedin was also approved as anticancer drug in Europe. The main problem in marine drug discovery research is material supply problem. Up till now, strategies to overcome the problem are "Pharmaceutical aquaculture" of biologically active marine biota and chemical synthesis approach. Chemical synthesis approach is feasible solution to be used, especially when working with less complex structure of compounds. However, when working with structurally complex compounds where total or even semi synthesis was very difficult to be provided, aquaculture can be a solution. Currently, the use of microbiology, biochemistry, genetic, bioinformatics, genomic and meta-genomic has been intensifying in order to have a better result in marine natural product drug discovery. As chemical synthesis needs an expensive investment of advanced technology and highly skilled human resources, thus pharmaceutical aquaculture is more practicable to overcome the material supply insufficiency in Indonesia. Up till now, many Indonesian marine bioprospectors have been working with culturable marine microorganism to produce bioactive compounds and some others starting to work with genomic and metagenomic-based drug discovery.

Keywords: Marine biotechnology, marine drug discovery, aquaculture, chemical synthesis

ABSTRAK

Kekayaan hayati laut menjadi sumber yang menjanjikan dalam kegiatan pencarian senyawa kimia baru dengan aktifitas farmakologi yang unggul sebagai kandidat obat kanker, peradangan, infeksi bakteri dan parasit, serta berbagai penyakit lainnya. Penemuan senyawa obat baru dari laut merupakan salah satu bidang penting dalam bioteknologi kelautan. Hingga saat ini, beberapa obat yang dikembangkan dari senyawa bahan alam laut telah disetujui penggunaannya; dua diantaranya adalah Ziconotide dan Trabectedin. Pada tahun 2004, Ziconotide telah disetujui penggunaannya sebagai obat pereda sakit di Amerika Serikat dan Eropa. Kemudian, pada tahun 2007, Trabectedin juga disetujui untuk digunakan sebagai obat antikanker di Eropa. Masalah utama dalam pengembangan senyawa obat dari laut adalah masalah pasokan bahan baku. Dua strategi yang saat ini digunakan untuk mengatasi masalah tersebut adalah dengan budidaya biota laut penghasil senyawa kimia aktif dan dengan pendekatan sintesis kimia. Ketika bekerja dengan struktur senyawa kimia yang tidak terlalu kompleks, pendekatan sintesis kimia dapat menjadi solusi untuk produksi senyawa kimia tersebut. Namun, ketika bekerja dengan senyawa kimia kompleks yang sulit untuk dilakukan sintesis total atau semi sintesis, maka budidaya dapat menjadi solusi. Saat ini, berbagai bidang ilmu seperti mikrobiologi, biokimia, genetika, bioinformatika, genomika dan metagenomika semakin intensif dikembangkan untuk mendukung usaha penemuan senyawa obat baru dari laut. Karena sintesis kimia membutuhkan investasi yang mahal terutama untuk teknologi canggih dan sumber daya manusia yang ahli, maka budidaya biota laut penghasil bahan farmasi menjadi solusi yang lebih praktis untuk mengatasi masalah pasokan bahan farmasi tersebut. Saat ini, banyak peneliti bioprospeksi kelautan Indonesia bekerja dengan mikroorganisme laut yang dapat dikultur untuk menghasilkan senyawa bioaktif dan sebagian kecil telah memulai penelitian genomik dan metagenomik sebagai usaha untuk menemukan bahan obat dari laut.

Kata kunci: bioteknologi kelautan, pencarian obat dari laut, budidaya, sintesis kimia

INTRODUCTION

Since the last decade, marine biotechnology has become scientifically fascinating area. Marine biotechnology covers wide ranges disciplines of science, including aquaculture, developmental biology, bioremediation, environmental management, biochemistry, biopolymers, molecular biology, genetics, transgenic animal and marine drug discovery (Gal & Halvorson, 1998; Gal & Ulber, 2005). Among those areas, aquaculture and marine drug discovery are currently become the raising stars in marine biotechnology.

Biotechnology in sustainable aquaculture and fisheries is well established and highly successful to support the world food security (European Science Foundation-Marine Board, 2001). Molecular biology, genetics, and other sciences in marine biotechnology play an important role for that achievement. As an example, gene transfer technology was used to enhance the growth of fish. In order to cultivate a fast-growing red sea bream, an economical fish species in China, a gene construction containing promoter gene of antifreeze protein (AFP) and salmon growth hormone cDNA was introduced into the fish by electroporation method (Zhang et al., 1998). Another example of the use of molecular biology technique in aquaculture is the development of DNA vaccines for aquaculture. Heppell et al. (1998) reported that DNA vaccines are safe, inexpensive and efficient to be used in aquaculture industry.

Another rising area in marine biotechnology is marine natural products (marine drug discovery). A significant number of drugs candidates have yielded from marine drugs discovery activity. The 2004 marine natural products review lists reported that 20 marine natural products or its analogs were in clinical trial phase (Newman & Cragg, 2004). Moreover, there were several marine-derived drugs that have already been approved. In 1963, a chemical synthetic drug of cytosine arabinoside which is a combination of cytosine base and arabinose sugar (the structure was first isolated from a Caribbean sponge *Cryptotethya crypta)* was marketed as antileukaemic drug (Kornprobst, 2010). Another marine-derived drug that currently is being marketed is Ziconotide. Ziconotide is a peptide discovered from cone snail that was approved as a pain treatment drug in the United States in 2004. Then, Trabectedin, a marine-derived anticancer drug was also approved to be used in Europe in 2007 (Molinski et al., 2009).

Those successfully marketed-marine derived drugs showed that marine environment is a rich source for drug discovery. Moreover, our earth surface was 70% covered by oceans (Dahuri, 2003), thus it can be estimated that marine biological diversity is much more abundance compare to terrestrial biological diversity. The biological diversity-rich marine environment gives us more promising opportunity to discover a pharmacologically active novel compounds from it.

This review will examine marine drug discovery as one of frontiers in emerging biotechnology. It will cover the history, current status of marine drug discovery, the main problem associated with marine drug discovery and the possible solutions, case study of two recently approved marine-derived drugs and will also cover about the current status of marine drugs discovery activity in Indonesia.

Drugs from the Sea

Biodiversity equals with chemical diversity (Williams, 2006). A recent study of National Institute of Health (USA) confirmed that natural products (secondary metabolites) are still the most effective sources of new chemical structures for developing new drug candidates (Williams, 2006). Terrestrial sources, plants and microorganisms, have been heavily being exploited, thus it only produces fewer number of novel chemical structural types. On the other hand, marine environment provides us with a wealth biological diversity, from which many biologically active compounds were discovered (Proksch et al., 2006). Moreover, since the metabolic system of marine organisms is different from terrestrial organisms', marine organisms take place as unique source of novel bioactive chemical structures. Marine invertebrates, such as sponges, bryozoan and tunicates, have been proven to be a good source of novel compounds with interesting pharmacological activity such as anti-tumor, anti-microbial and anti-virus (Pabel et al., 2003).

Marine invertebrates were 'ancient' organism that have successfully adapted to the extreme marine environmental conditions (high concentration of salt, tides, extreme temperature, high pressure, competition to other organisms or predators). In order to survive from those environmental stress conditions, marine invertebrates require specific adaptation strategies (i.e. by producing chemical 'weapons') leading to unique natural product substances (Haefner, 2003; Proksch et al., 2006). That chemical substances produced by marine invertebrate becomes a unique source of novel compounds with interesting biological activity.

The 'drugs from the sea' concept was firstly catch the attention in the beginning of 1951 when Werner Bergmann published reports of *ribo*-pentosyl nucleosides isolated from marine sponges which then led to the development of anticancer properties of

ara-A (vidarabine) and ara-C (cytarabine) (Molinski et al., 2009). Marine drug discovery research was just taken seriously at 1960s when sizeable prostaglandin, an important mediator in fever, pain and inflammatory diseases, was discovered from marine gorgonian *Plexaura homomalla* (Weinheimer & Spraggins (1969) *in* Proksch et al., 2006). However, interest in marine drug discovery depended on the development of others technology, especially the technology to collecting samples from ocean resources (i.e. scuba diving) (Molinski et al., 2009). Thus, the first drug from the sea took long time to come.

Current Status of Marine Drug Discovery

Pharmacologically Active Compounds

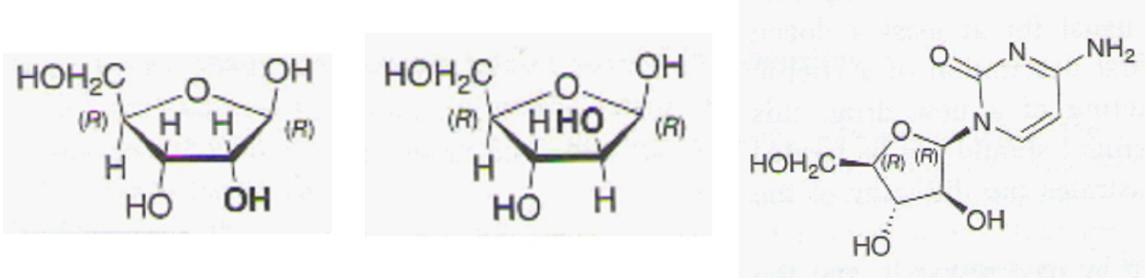
Up till now, there were several marine-derived drugs that have already been approved. The first success story of marine-derived drug is cephalosporin that has been marketed since 1964. Cephalosporin is an antibiotic that firstly isolated from microscopic fungus *Cephalosporium acremonium* in 1948. Currently, chepalosporins are produced by chemical synthetic (the 4th-generation cephalosporin). In 1999 the market of chepalosporin-drugs in the world was accounted $ 8.75 billion (Kornprobst, 2010).

In the beginning of 1950s, an American chemist Werner Bergmann isolated arabinose sugar from a Caribbean sponge *Cryptotethya crypta*. The structure of the arabinose is very similar to ribose sugar of human purine bases; the difference is only at one hydroxyl group position (Fig. 1). Based on that, an idea to chemically-synthesized cytosine arabinoside which is very similar to human cytosine deoxyribose was come up. The little difference between the chemically-synthesized cytosine arabinoside and cytosine deoxyribose (human base) is enough to kill the cancerous cell (Kornprobst, 2010). In 1963, a chemical synthetic drug of cytosine arabinoside (Ara-C; Fig. 1) which is a combination of cytosine base and arabinose sugar was marketed as antileukaemic drug by the Upjohn Company.

The new development of high throughput screening method, spectroscopy, analytical technology and pharmacology provide a strong effort on the development of marine drug discovery (Molinski et al., 2009). As previously mentioned, 2 hits of marine-derived drug compounds were recently approved. In 2004, Ziconotide was approved as pain treatment drugs in the United States. Then, in 2007, Trabectedin was also approved as anticancer drug in Europe (Molinski et al., 2009).

Mayer et al. (2009) made a review on the 2005-2006 marine pharmacology peer reviewed literature. During 2005-2006 there were 78 marine chemicals with pharmacological activities as anti-helmintic, anti-coagulant, anti-bacterial, anti-malarial, anti-tuberculosis, anti-protozoa and anti-viral. They also reported, approximately of 47 marine compounds were anti-inflammatory compounds, cardiovascular compounds, and compounds affecting immune and nervous systems. Moreover, the review also reported that 58 marine compounds have an ability to bind with various of molecular targets. For instance Amphezonol A, a polyketide compound isolated from marine algae, showed pharmacological activity as DNA-polymerase inhibitor.

Newman & Cragg (2004) made a review for list of marine natural products development. It was reported that 20 marine natural products or its analogs were in clinical trial phase (2 compounds were in phase III; 8 compounds were on phase II; and 10 compounds were on phase I). Most of that were pharmacologically active as anti cancer drugs (10 compounds), and some other were candidates for anti inflammation, asthma, alzheimer and pain drugs candidates. Research funds on marine drug discovery mainly go to the research to discover anticancer compounds (i.e. National Cancer Institute) which resulted in anticancer drugs candidate as mainly research hits (Proksch et al., 2006).



A. D-Ribose B. D-Arabinose C. Arabinosylcytosine (Ara-C)

Figure 1. The structure of human D-Ribose and D-Arabinose is very similar; the little difference is one hydroxyl group position (A and B). The structure of Ara-C (C). (Kornprobst, 2010).

PROBLEM IN MARINE DRUG DISCOVERY AND ALTERNATIVE SOLUTIONS

Main Problem in Marine Drug Discovery

The main problem in marine drug discovery research is material supply problem. The fact that marine invertebrate only produce a low yields of active compound become an obstacle to develop the promising biologically active compounds. As a case example, to obtain 1.4 g of Bryostatin-1, an anticancer drug candidate currently in phase II clinical trial, approximately 1 metric ton of *Bugula neritina* should be extracted (Proksch et al., 2006). Thus, it could risk the sustainability of the bryozoans *B. neritina.* Moreover, one of an important issue in bio-prospecting is how to minimize the impact to the environment (Hunt & Vincent, 2006). A reliable source of material for drugs development is essential. Thus, alternative solutions to overcome the problems are urgently needed. Some strategies have been developed as alternative solutions to this problem.

Alternative Solutions

1. Aquaculture for Sustainable Supplies of Marine-Derived Drugs Material (Yondelis™ / ET-743 Case Study)

"Pharmaceutical aquaculture" of biologically active marine invertebrates (i.e. sponges, bryozoans, tunicates and others) can be used as an alternative solution to overcome the material supply problem (Mendola et al., 2006). Mariculture of *Esteinascidia turbinata*, a tunicate from which an anticancer Yondelis™ was isolated, is a success example of how mariculture can be used to supply material for promising marine drugs candidate (Mendola et al., 2006). Below is an aquaculture case history of *Esteinascidia turbinata* which is cited from Mendola et al. (2006).

Esteinascidia turbinata is an ascidian (tunicate) which normally lives in shallow waters coastal. It can be found in Caribbean coastal throughout the year. In 1990, the trabectedin compound, isolated from *Esteinascidia turbinato*, was identified and characterized. Trabectedin (Yondelis™) is a cytotoxic compound with a broad spectrum of anti cancer activity. It has biological activity against various solid tumor cell lines, soft tissue sarcoma, breast, prostate, non small cell lung, melanoma, renal, and also ovarian cancer (Jimeno et al., 2004). Trabectedin (Yondelis ™) was also reported to have a unique anti cancer mechanism of action. It binds to the DNA minor groove with specificity of sequence and induces transcription inhibition with no effect to the transcription constitutive (Friedman et al., 2002 *in* Mendola et al., 2006). Trabectedin was also reported to inhibit the multidrugs resistant pathway activation. Trabectedin (Yondelis ™) was approved as anticancer drug in 2007.

Marine natural products isolated from tunicates, sponges or other marine invertebrate usually have a very complex structural complexity which are not feasible to be produced by total synthesis. In 1997, a total synthesis of Trabectedin (Yondelis ™) was completed. However, it was not sufficient to be the only source for clinical development needs. Thus, in 1997, PharmaMar, a pharmaceutical company developing Trabectedin decided to use natural sourcing as its main material resource for pre-clinical and clinical needs. At the same time, PharmaMar also intensified the efforts of making the chemical synthetic of Trabectedin (Yondelis ™).

The aquafarming of *Esteinascidia turbinata* was done using 2 methodologies. Firstly, it was aquacultured in the seafarms using artificial structures (i.e. long lines, nets) in which species adapted vegetative growth habitat. The second method is by aquafarming it in inland facilities using tanks and ponds equipped with artificial structures as used in seafarms. Both of the culture methods showed a high potential of *Esteinascidia turbinata* vegetative growth. However, inland aquaculture system, especially that established at indoor hatcheries, was operationally easier to control the salinity, water flow, temperature, algae blooms, *etc* compared to seafarms.

The biomass production of *Esteinascidia turbinata* in one single year is approximately reached 80 metrics ton. Thus, the aquaculture of *Esteinascidia turbinata* could supply the material for Trabectedin (Yondelis ™) extract production for clinical trial needs. However, in 2004, PharmaMar decided to switch the source of Trabectedin (Yondelis ™) production from natural resources to semi-synthetic source. The decision was related to the cheaper cost production of synthetic Trabectedin (Yondelis ™). The isolation of Trabectedin (Yondelis ™) from tunicate-*Esteinascidia turbinata* involved a complex chemical extraction process (extraction and purification process) which employing organic solvents and multiple steps of chromatographic purification. On the other hand, the production of chemically semi-synthetic Trabectedin (Yondelis ™) was relatively economical and easy. The synthetic production of Trabectedin (Yondelis ™) was started with producing the fermentation product of cyanosafracin B from *Pseudomonas flourescens*, which then chemically converted into Trabectedin through 18 steps.

As previously mentioned, marine natural products usually have a very complex structure which difficult to be produced by total or semi synthesis. However,

this 'Yondelis™' case study showed us that 'pharmaceutical aquaculture' can be implemented to provide sufficient source for the development of marine-derived drugs or at least sufficient source for clinical development needs. Once the chemically synthetic drugs can be produced, economical calculations can be made. Whichever is more economical, providing the drugs through aquaculture or chemical synthesis.

Chemical Synthesis of Marine-Derived Drugs (Ziconotide Case Study)

Developing chemical synthesis is the main approach that currently used to produce marine-derived drugs candidates. One of case example of the success used of this approach is the chemical synthesis of ziconotide, a neuron specific analgesic isolated from *Conus magus* (Proksch et al., 2006). Ziconotide is the first marine-derived drug that was approved by Food and Drugs Administration USA and European Commission (Molinski et al., 2009). The peptide was launched in the USA under the trade name 'Prialt'. Ziconotide plays as an analgesic for the chronic pain treatment for AIDS and cancer (Haefner, 2003).

The lead compound of ziconotide was ω-conotoxin MVIIA which was isolated from cone snail. Reported by Molinski et al. (2009), ω-conotoxin MVIIA is a polycationic peptide consisted of 25 linier amino acids with 6 cystein residues linked by 3 dissulfide bridges which stabilize its three dimensional structures. The complete chemical synthesis of ω-conotoxin MVIIA was done on 1987. Molinski et al. (2009) also reported that the mechanism of action of ω-conotoxin MVIIA is by specifically blocking the complex N-type voltage-sensitive calcium channels (NVSCCs).

Chemical synthesis approach is feasible solution to be used, especially when working with less complex structure of compounds. Once the chemical synthesis is successfully achieved, a biologically active compound can be produced economically. However, when working with structurally complex compounds where total or even semi synthesis was very difficult to be provided, aquaculture can be a solution.

ANOTHER EMERGING APPROACH IN MARINE DRUG DISCOVERY

In order to have a better result in marine natural product drug discovery, some new approaches have also been developed. The use of microbiology, biochemistry, genetic, bioinformatics, genomic and metagenomic have been intensifying.

Some research findings showed that the active compounds isolated from marine invertebrate have structure similarities with compounds isolated from marine microorganisms. Those findings support the hypothesis that the bioactive compounds isolated from marine invertebrate (i.e. sponges) were originating from endosymbiotic microorganism (Hill et al., 2005; Proksch et al., 2006). Numerous data showed that the bioactive compounds are produced either by the symbiont or by the association between the host and symbiont (Kornprobst, 2010). As an example, Sorbicillactone A is a bioactive compound produced by marine fungi *Penicillium chrysogenum* that live in symbiosis with marine sponge *Ircinia fasciculate*. Sorbicillactone A showed selective bioactivity against leukemia cells and had ability to protect human T cells against the cytopathic effects of HIV-1 (Bhatnagar & Kim, 2010).

However, it is widely accepted that the majority (>99%) of marine microorganisms cannot be cultured using traditional culturing method (Kennedy et al., 2010). Thus, the traditional culturing technique that is used to produce bioactive secondary metabolites from cultured microorganisms most likely missed the majority of bacterial-metabolites that exist in the nature (Banik & Brady, 2010).

A new strategy of culture-independent method (metagenomic) to explore the untapped reservoir of marine microbial chemical diversity has been developed since 1990s. Metagenomics is basically a modern genomics approach to isolate the DNA of microbial communities directly from their natural environments (environmental DNA/eDNA), therefore difficulties associated with culturing the microbes can be avoided (Chen & Pachter, 2005). Since the genetic information that encoding the secondary metabolites produced by microorganism is typically clustered on the microorganisms' chromosomes, hence it is possible to predict the complete gene clusters of secondary metabolites biosynthesis on those organisms, which might provide a renewable source of the secondary metabolites (Banik & Brady, 2010). Once a gene has been identified, the genetic information can be used for compound production.

PRESENT STATUS OF MARINE DRUGS DISCOVERY IN INDONESIA

Indonesia, a tropical country with 5.8 million km square of marine waters, is a nation with the highest marine biological diversity in the world. Indonesia possesses 27.2% of the world's flora and fauna. Approximately 12% mammalian, 23.8% amphibian, 31.8% reptilian, 44.7% fish, 40% mollusc and 8.6 % algae of the whole species in the world are found in Indonesia (Dahuri, 2003). It was also reported that

Indonesian ocean has a large variety of biota, including 38 mangrove species, 210 soft corals species, 350 hard coral species, 350 gorgonian species, 745 echinoderm species, 782 algae species, > 850 sponge species, and hundred thousands of other macro-micro biota which are not known yet (Mossa et al., 1996). That rich marine biodiversity gives an opportunity for many researchers in the world, especially Indonesian researchers, to explore the use and the benefit of Indonesian marine resources through bioprospecting research.

Marine natural products research in Indonesia was started by Corney et.al. in the late of 1980's, who isolated two new cytotoxic compounds, laulimalide and isolaulimalid from sponge *Hyatella* sp. Following the discovery of laulimalide and isolaulimalide, tens of new compounds were then discovered from Indonesian marine invertebrates (Dewi et al., 2008). Among them are elenic acid, a topoisomerase II inhibitor from Indonesian sponge species *Plakinastrella* sp. and cyclic peptide barangamide with bioactivity as anti-cancer and HIV inhibitor isolated from Indonesian sponge *Theonella swinhoei* (Faulkner, 2001). Nevertheless, most of the discovery of new compounds isolated from Indonesian specimen were not discovered by Indonesian researcher. The fact that most of new bioactive compounds isolated from Indonesian marine organisms were discovered by non-Indonesian researcher showed that there are many obstacles and challenges in the area of marine drug discovery in Indonesia (Dewi, 2008; Chasanah, 2009a).

Up to present, Indonesian researchers from national research institutes and universities in Indonesia have been conducting marine bioprospecting research in small scale. However, insufficient source of bioactive compounds is a substantial problem for developing a potential bioactive hit of marine natural products into drug in Indonesia. In many cases, once Indonesian researcher got a hit of potent marine bioactive compounds, due to insufficient amount of the active compound, the research could not be proceed into the next phase of drug discovery, including hit confirmation and pre clinical development. As a result, up till now no marine-derived compound isolated from Indonesian resources comes into the drugs development phase. As previously described, chemical synthesis and pharmaceutical aquaculture are feasible approaches to overcome the material supply problem for marine-derived drug development. However, chemical synthesis needs an expensive investment of advanced technology and highly skilled human resources. On the other hand, lack of research funds and infrastructures is one of classic problems in the development of marine drugs discovery activity in Indonesia. Thus, pharmaceutical aquaculture is more practicable to overcome the material supply insufficiency in Indonesia.

Numerous data showed that marine bioactive compounds are produced either by the symbiont or by the association between the host and symbiont (Kornprobst, 2010). Along with the development of genomic and metagenomic-based drug discovery, some Indonesian marine bioprospectors are currently starting to work in this research area. While many others have been working with marine microorganism that living as endosymbiont of marine organism. Chasanah et al. (2009a) and Nursid et al. (2011) conducted bioprospecting research of bioactive compounds produced by Indonesian marine-derived fungi and reveal several prospecting fungi species that produce bioactive compounds, mainly with antitumor activity. Fungi *Emericella nidulans* which associated with ascidia *Aplidium longithorax* collected from Wakatobi waters produced bioactive compound emestrin diketopiperazine. The emestrin diketopiperazine derivative showed strong antitumor activity through apoptosis induction mechanism (Nursid et al., 2011). As marine microorganisms can be cultured using traditional culturing method to produce bioactive secondary metabolites, thus material supply problem can be overcomed.

CONCLUSION

Marine drug discovery is a rising area in marine biotechnology. Several hits of marine-derived drug compounds were approved; two of them are Ziconotide as pain treatment drugs and Trabectedin as anticancer drug. The main problem in marine drug discovery research is material supply problem. Current strategies to overcome the problem are "Pharmaceutical aquaculture" of biologically active marine biota and chemical synthesis approach. Chemical synthesis approach is feasible solution to be used, especially when working with less complex structure of compounds. However, when working with structurally complex compounds where total or even semi synthesis was very difficult to be provided, aquaculture can be a solution. The use of microbiology, biochemistry, genetic, bioinformatic, genomic and metagenomic has been intensifying in order to have a better result in marine natural product drug discovery. As chemical synthesis needs an expensive investment of advanced technology and highly skilled human resources, thus pharmaceutical aquaculture is more practicable to overcome the material supply insufficiency in Indonesia. Up till now, many Indonesian marine bioprospectors have been working with culturable marine microorganism to produce bioactive

compounds and some others starting to work with genomic and metagenomic-based drug discovery.

REFERENCES

Banik, J. J. and Brady, S. F. 2010. Recent application of metagenomic approaches towards the discovery of antimicrobials and other bioactive small molecules. *Curr Opin Microbiol.* 13(5): 603-609.

Bhatnagar, I. and Kim, S. 2010. Marine antitumor drugs: status, shortfalls and strategies. *Mar. Drugs*. 8: 2702-2720.

Chasanah, E. 2009a. Marine biodiscovery research in indonesia : challenges and rewards. *Journal of Coastal Development*. 12(1): 1-12.

Chasanah, E., Januar, H. I., Irianto, H. E., Bourne, D., Liptrot, C., and Wright, A. 2009b. Screening of anticancer activity of fungi derived from Indonesian marine *sponges*. *J. Marine and Fisheries Postharvest and Biotechnology Special Edition in Conjunction with World Ocean Conference 2009*. 4: 1-8.

Chen, K. and Pachter, L. 2005. Bioinformatics for whole-genome shotgun sequencing of microbial communities. *PLOS Computational Biology*. 1(2): 106-112.

Dahuri, R. 2003. *Keanekaragaman Hayati Laut*, Aset Pembangunan Berkelanjutan Indonesia. PT Gramedia Pustaka Utama. Jakarta.

Dewi, A. S., Tarman, K., and Uria, A. R. 2008. Marine natural products: prospects and impacts on the sustainable development in Indonesia. *Proceeding of Indonesian Students' Scientific Meeting, Delft, The Netherlands.* May 2008. pp: 54-63.

European Science Foundation-Marine Board. 2001. *Marine biotechnology: a European strategy for marine biotechnology*. Irelend: European Science Foundation.

Faulkner, D. J. 2001. Marine Natural Products. *Nat. Prod. Rep*. 18: 1-49.

Gal, Y. L. and Halvorson, H. O. (Eds.). 1998. *New development in marine biotechnology*. New York: Plenum Press.

Gal, Y. L. and Ulber, R. (Eds.). 2005. *Marine Biotechnology I*. Berlin: Springer-Verlag.

Haefner, B. 2003. Drugs from the deep: marine natural products as drug candidates. *DDT*. 8(12), 536-544.

Heppell, J., Wu, T., Lorenzen, N., Ellis, A.E., Efler, S.M., Armstrong, N. K., Schorr, J., and Davis, H. L. 1998. *Development of DNA vaccines for aquaculture*. In Gal, Y. L., and Halvorson, H. O. (Eds.), *New development in marine biotechnology*. New York: Plenum Press.

Hill, R. T., Hamann, M. T., Enticknap, J., and Rao, K. V. 2005. Kahalalide-producing bacteria and methods of identifying kahalalide-producing bacteria and preparing kahalalides. *PCR Int. Appl.* 41.

Hunt, B. and Vincent, A. C. J. 2006. Scale and sustainability of marine bioprospecting for pharmaceuticals. *Ambio*. 35(2): 57-64.

Jimeno, J., Lopez-Martin, J. A., Ruiz-Casado, A., Izquierdo, M. A., Scheuer, P. J., and Rinehart, K. 2004. Progress in the clinical development of new marine-derived anticancer compounds. *Anti-Cancer Drugs.* 15: 321-329.

Kennedy, J., Flemer, B., Jackson, S. A., Lejon, D. P. H., Morissey, J. P., O'Gara, F., and Dobson, A. D. W. 2010. Marine metagenomics: new tools for the study and exploitation of marine microbial metabolism. *Mar. Drugs.* 8: 608-628. Doi:10.3390/md8030608

Kornprobst, J. 2010. *Encyclopedia of marine natural products volume 1: general aspects, microorganisms, algae and fungi*. Wiley-VCH Verlag GmbH & Co. Weinheim, Germany. pp. 37-57.

Mayer, A. M. S., Rodriguez, A. D., Berlinck, R. G. S., and Hamann, M. T. 2009. Marine pharmacology in 2005-2006: Marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. *Biochimica et Biophysica Acta*. 1790: 283-308.

Mendola, D., Lozano, A. N., Duckworth, A. R., and Osinga, R. 2006. The promise of aquaculture for delivering sustainable supplies of new drugs from the sea: examples from in-sea, and tank-based invertebrate culture projects from around the world. In Proksch, P., and Muller, W. E. G. (Ed.), *Frontiers in marine biotechnology*. England: Horizon Bioscience. pp. 21-27.

Molinski, T. F., Dalisay, D. S., Lievens, S. L., and Saludes, J. P. 2009. Drug development from marine natural products. *Nature Reviews.* 8: 69-85.

Moosa, M.K., Dahuri, R., Hutomo, M., Suwelo, I.S., and Salim, S. 1996. Indonesian country study on integrated coastal and marine biodiversity management. Ministry of State for Environment Republic of Indonesia in Cooperation With Directorate for Nature Management Kingdom of Norway. Jakarta.

Newman, D. J., and Cragg, G. M. 2004. Marine natural products and related compounds in clinical and advanced preclinical trials. *J. Nat. Prod*. 67: 1216-1238.

Nursid, M., Chasanah, E., Murwantoko, and Wahyuono, S. 2011. Isolasi senyawa sitotoksik dari kapang *Emericella nidulans*. *Jurnal Pasca Panen dan Bioteknologi Kelautan dan Perikanan*. 6(2): 119-130

Pabel, C.T., Joachim, V., Wilde, C., Franke, P., Hofemeister, J., Adler, B., Bringmann, G., Hacker, J., and Hentschel, V. 2003. Antimicrobial activities and matrix assisted laser desorption/ ionization mass spectrometry of Baccilus isolated from the marine sponge *Aplysina aerophoba*. *Marine Biotechnology*. 424-434.

Proksch, P., Edrada, R., and Lin, W. H. 2006. Implication of marine biotechnology on drug discovery. In Proksch, P., and Muller, W. E. G. (Ed.), *Frontiers in*

marine biotechnology. England: Horizon Bioscience. pp. 1-19.

Williams, D. 2006. *Coral reefs to clinical trials: Bio-prospecting for drugs from the sea.*. Proceeding of International Seminar and Workshop: Marine Biodiversity and Their Potential for Developing Biopharmaceutical Industry in Indonesia. Jakarta, May 17-18 2006. Agency for Marine and Fisheries Research.

Zhang, P., Xu, Y., Zongzhu, L., Xiang, Y., Du, S., and Hew, C. L. 1998. Gene transfer in red sea bream (*Pagrosomus major*). In Gal, Y. L., and Halvorson, H. O. (Eds.), *New development in marine biotechnology* New York: Plenum Press. pp. 15-18

INFORMASI PUBLIKASI PERPUSTAKAAN BALAI BESAR PENELITIAN DAN PENGEMBANGAN PENGOLAHAN PRODUK DAN BIOTEKNOLOGI KELAUTAN DAN PERIKANAN

BUKU BARU

1. The Microbiology of Safe Food / BL/ Stephen / 2010
2. Sanitation: Cleaning and Disinfection in The Food Industry / Jian / 2010 / JW
3. Seafood Ecolabeling / 2008 / Phillips / Blw
4. Handbook of Seafood Quality, Safety and Health Application / BLW / Kazuo / 2011
5. Fish Processing: Sustainability & New Opportunities / WP / Hall / 2011
6. In Pack Processes Food: Improving Quality / WP / Phillip / 2008
7. Environmental Effects on Seafood Availability, Safety and Quality / WP / Kozon / 2011
8. Fish Canning Handbook / 2010 / WI / Bratt
9. Environmentally Compatible Food Packaging / WP / Chiellini / New
10. Microbial Safety of Fresh Product / Blw / Xuetong / 2009
11. Nondestructive Evaluation of Food Quality…2009/spr/by:jha
12. Control of Fish Quality 4th ed / FNB / Connell
13. Principles of Food Toxicology / Pussa / CRC / 2008
14. Food Safety For the 21st Century Managing HACCP … / 2011 / WI / Wallance
15. Introduction to Food Toxicology 2ed / Takayuki / AP
16. Principles of Microbiological of Troubleshooting in The Indus Food Process Environ /10/Spr/Jeffrey
17. Ingredients in Meat Products: Properties, Functionality and Application / Spr / 2009 / Tarte
18. Handbook of Firezen Food Processing and Packaging 2ed / 2012 / Sun / CRC
19. Jurnal Pengelolaan Hasil Perikanan Indonesia Vol.13 no.2 Tahun 2010, Vol.14 no.1 Tahun 2011 (dari Masyarakat Pengolahan Hasil Perikanan Indonesia/MPHPI)
20. BAWAL Vol.3 No.4, 2011 (dari Pusat Penelitian Pengelolaan Perikanan dan Konservasi Sumber Daya Ikan)
21. Jurnal Standarisasi Vol.13 No. 1 dan 2, Tahun 2011 (dari BSN)
22. Mina bahari Edisi Juni, Juli, November 2011 (dari Pusdatin)
23. TROBOS edisi Agustus, Oktober, November, Desember 2011 dan Januari 2012 (dari PT JAPFA Comfeed Indonesia Tbk)
24. Jornal Pustakawan Indonesia Vol.10 no.2, 2010 (Perpustakaan IPB)
25. SINERGI edisi III/2011 (ITJEN KKP)
26. Warta Pasar Ikan edisi Agustus 2011 vol.96 (Ditjen P2HP)
27. BUDIDAYA Tahun ke- 9 edisi 16,17,19 Tahun 2011 (Dirjen Budidaya)
28. Jurnal Penelitian Perikanan Indonesia (Puslit pengembangan konservasi sumberdaya ikan)
29. Buletin Teknik Litkayasa Sumberdaya Penangkapan (Puslit pengembangan konservasi sumberdaya ikan)
30. Indonesian Fisheries Research Journal (Puslit pengembangan konservasi sumberdaya ikan)