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Distribution and diversity of marine natural products from Indonesian marine organisms

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ABSTRACT

Objective: To study the distribution and diversity of species and isolated molecules, according to their structure classes, from Indonesian marine organisms.

Methods: This study was performed by using the SciFinder® database, MarinLit and references from relevant articles from 1980 to 2014 which collected all the scientific publications dealing with the isolation of chemical compounds from Indonesian marine macroorganisms and microorganisms.

Results: The discovery of novel compounds from Indonesian marine organisms gave us a result of a total of 78 papers. Alkaloids, terpenoids and peptides (84, 67 and 15 new compounds, respectively) represented the three main chemical classes of compounds discovered from Indonesian marine organisms, and together with the other chemical classes showed a range of biological activities.

Conclusions: The new marine compounds are mainly from sponges and soft corals. Alkaloids, terpenoids and peptides are the most prolific compounds isolated from Indonesian marine organisms. Most marine natural products from Indonesian organisms have been screened for anticancer or cytotoxicity activities.

1. Introduction

Natural products have proven to be rich sources of bioactive leading compounds for drug discovery. In the past 50 years, marine organisms have been the focus of a worldwide effort to define the natural products of the marine environment, mainly as a result in the improvement of collection techniques, such as self-contained underwater breathing apparatus diving[1,2]. Oceans, which cover more than 70% of the earth's surface, represent a virtually untapped resource for the discovery of potential new drugs. To date, over 24000 secondary metabolites, *i.e.* small molecule marine natural products, which hold high potentials for pharmacologically important leading drugs, have been isolated[3].

Drug development from marine biological diversity is a part of an activity called marine bioprospecting. Seven marine natural products

or derivatives in different phases of the clinical pipeline (Table 1) have been approved by US Food and Drug Administration (FDA) or European Medicines Agency (EMA)[4], while twelve compounds are in Phase I, II and III of the clinical development and, hopefully, they will soon enrich the marine clinical and pharmaceutical pipeline. Each of these classes of marine bioproducts has a potential multi-billion dollar market value. For example, cytarabine and vidarabine were estimated at \$93 million each in 2007[5] and according to a market report by TechNavio, the marine biotech market is anticipated to grow at a compound annual growth rate of 3.82% over the period 2012–2016[6].

Table 1

FDA and EMA approved marine drugs.

Clinical status	Compound	Marine organism	Therapeutic area
FDA-approved	Brentuximabvedotin	Mollusk/Cyanobacterium	Cancer
	Cytarabine (Ara-C)	Sponge <i>Tethya crypta</i>	Cancer
	Omega-3-acid ethyl esters	Fish	Hypertiglyceridemia
	Ziconotide	Cone snail	Pain
	Eribulin Mesylate	Sponge <i>Halicondria okadai</i>	Cancer
EMA-approved	Vidarabine	Sponge <i>Tethya crypta</i>	Antiviral
	Trabectedin	Tunicate <i>Ecteinascidia turbinata</i>	Cancer

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Figure 1 shows the total number of new compounds isolated from the top ten countries. It has been found that at least 20 new compounds were isolated from Japanese sponge samples each year from 2001 to 2010, with the highest output occurring in 2004 and 2005 (46 new compounds). From 2006 to 2009, at least 20 compounds were found each year in Indonesia[7].

Indonesia, the world's largest archipelagic state, is found between 6°–10° N and 95°–142° E. It is well-known as a country of mega-diversity, consists of about 17 500 islands and has a coastline of 81 000 km. About 78% of Indonesian territory is covered by ocean from Sabang to Merauke and more than 70% Indonesians live in coastal regions[8]. The first marine compound, named laulimalide, isolated from Indonesian marine organisms was discovered by Corney *et al.* in 1980[9].

To date, more than 100 marine compounds have been isolated from Indonesian marine organisms, such as sponges, soft corals, tunicate, algae, and reported in more than 70 publications[10]. However, although Indonesia is an excellent source of marine organisms, most of their studies were conducted by scientists in other countries. One of the pharmaceutical products from Indonesia that has successfully approved by the FDA is the pain medication Prialt, developed by the Elan Corporation. It has been reported that the revenue from the sales of Prialt reached \$6.1 million in 2010. At the moment, however, it remains unclear whether there have been any benefit-sharing arrangements related to the commercial application of marine genetic resources collected from Indonesia[11].

2. Materials and methods

This study was performed by using the SciFinder® database, MarinLit and references from relevant articles from 1980 until 2014, which collected all the scientific publications dealing with the isolation of chemical compounds from Indonesian marine

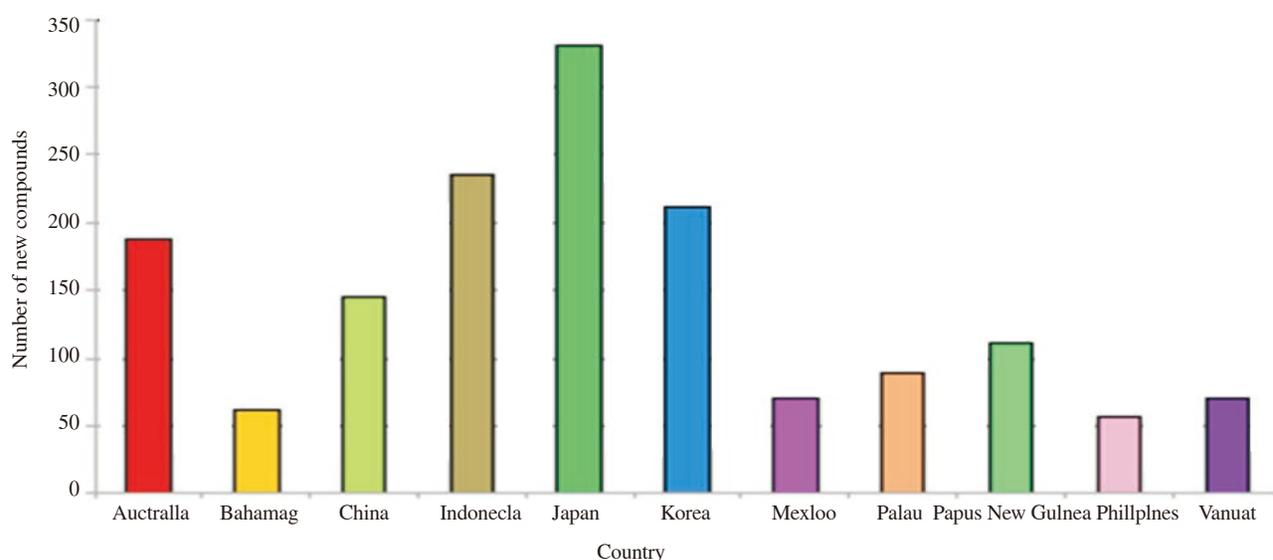


Figure 1. The total number of new compounds isolated from marine sponges from the top 10 source countries from 2001 to 2010[7].

macroorganisms and microorganisms. Based on their chemical structure, these natural products are divided into terpenoids, steroids (including steroidal saponins), alkaloids and lipids. We used biological classification to assign organisms to three major biological classes, marine microorganisms (bacteria and fungi), marine invertebrates (gorgonians, sponges, soft corals, ascidians, sea pens) and marine algae.

3. Results

3.1 Species distribution

Figure 2 shows the number of publications describing the isolation of new marine natural products from different phyla of Indonesian marine organisms. The organisms which have been the object of the greatest number of investigations are marine invertebrates including sponges and soft corals.

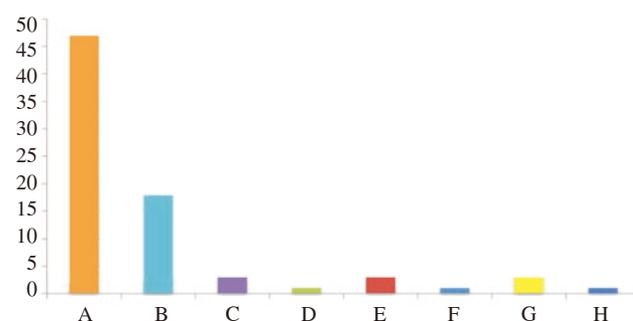


Figure 2. The number of publications describing the isolation of new marine natural products from different phyla of Indonesian marine organisms.

A: Sponges; B: Soft coral; C: Gorgonian; D: Sea pen; E: Ascidian; F: Algae; G: Microorganisms; H: Tunicate.

Marine invertebrates, which are plentiful in the Indo-Pacific regions including Indonesia, are rich in secondary metabolites and are becoming targets for the continuing search for bioactive compounds[12]. Since the early days of research into marine natural

products in the 1960s, sponges have famously yielded the largest number of new metabolites reported per year compared to any other known marine plant or animal phylum[7]. Numerous ecological studies have shown that to survive in the complicated marine environment, most sponge species have active secondary metabolites to defend against predation, microbial infections, biofouling, and overgrowth by other sessile organisms. Furthermore, recent studies demonstrate that the microbial symbionts in sponges could play a more important role in the production of natural products.

Soft corals belonging to the family Alcyoniidae are the dominant reef dwelling octocorals in the Indo-West Pacific. These organisms are known to produce a wide array of secondary metabolites, particularly diterpenoids and steroids. Since 1997–2014, more than 20 publications have reported on the bioactive compounds from Indonesian soft corals such as *Cladiella* sp., *Lobophytum* sp. and *Sinularia* sp. Putra's work in 2009–2012, has contributed eleven new compounds, belonging to different structural classes, some of which possess interesting pharmacological activities[13].

The discovery of novel compounds from Indonesian sea pens, tunicates and algae are much rarer, as indicated by the fact that until now only one publication has described novel compounds from them. Almost 90% of new marine natural products from Indonesian marine organisms were collected from Eastern Indonesia (North Sulawesi and South Sulawesi). This search was conducted in January 2015 and gave us a result of a total of 78 papers about the isolation of new compounds from marine organisms.

Sponges are currently divided into four distinct classes, 25 orders, 128 families and 680 genera. As reported in Figure 3, the orders of sponges that have been the object of the greatest number of investigations are Haplosclerida, Dictyocetida, Poecilosclerida (11, 9 and 6 publications, respectively). This result is not surprising, since there are also the orders including the greatest number of species.

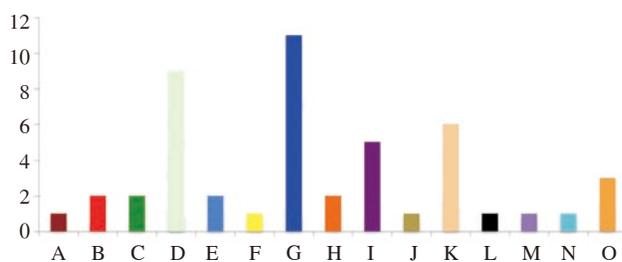


Figure 3. Total number of new compounds isolated from different orders of marine sponges.

A: Agelasida; B: Clathrinida; C: Dendroceratida; D: Dictyocetida; E: Hadlichondrida; F: Halichondrida; G: Haplosclerida; H: Homosclerophorida; I: Tetractinellida; J: Lithistida; K: Poecilosclerida; L: Verongida; M: Stolidobranchia; N: Scopalinida; O: Unknown.

3.2. Chemical compounds isolated from marine organisms

Figure 4 shows the distribution of the isolated molecules according to their structure classes. The analyzed data has shown

alkaloids, terpenoids and peptides (84, 67 and 15 new compounds, respectively) were the major compounds isolated from Indonesian marine organisms.

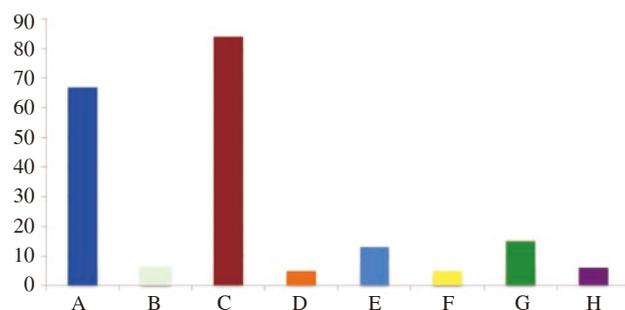


Figure 4. Distribution of isolated molecules according to their structure classes.

A: Terpenoid; B: Steroid; C: Alkaloid; D: Ether/Ketal; E: pheno/Quinone; F: Lactone; G: Peptide; H: Lipid.

Among the numerous classes of natural products isolated from Indonesian sponges over the years, alkaloids, terpenoids and peptides have attracted particularly wide attention due to their unusual structural features, often unprecedented or with few terrestrial counterparts, as well as their potent activities which make several of these metabolites of interest to developers of new drugs against human diseases.

More than half of the alkaloids isolated from Indonesian marine organisms were obtained from sponges such as *Leucteta chagosensis*, *Agelas linnaei*, *Acanthostrongylophora* sp and major classes of sponge-derived alkaloids, imidazole alkaloid, brominated pyrrole and manzamine alkaloid. Most of the peptides isolated from marine sponges show potent cytotoxic or antimicrobial qualities, are specific ion-channel blockers, or display other properties with novel chemical structures associated with original mechanisms of pharmacological activity. Barangamide A is the first marine peptide isolated from Indonesia marine sponges *Theonella swinhoei*.

During the last decade, Indonesian soft corals such as *Sinularia*, *Lobophytum*, *Nephthea* and *Cladiella*, have yielded many new structure classes, one is terpenes, dominated by the cembrane-type of diterpenes, and they are believed to play an important role within the chemical defense arsenal against other reef organisms. These metabolites were recently shown to possess a range of biological activities such as antimicrobial, anti-inflammatory, cytotoxic and several others.

3.3 Distribution of biological activities

In recent years marine organisms have been screened for a variety of compounds with different biological activities. Figure 5 shows that the number of compounds and their biological activities. Anticancer or cytotoxicity activity was exhibited by the highest number of compounds, at 34 papers, more than half of the reported activity. Among all organisms screened, sponges represent one of the most promising sources of marine bioactive compounds

particularly for anticancer or cytotoxicity activity. Anticancer activity has been observed from samples of Haplosclerida, Dictyoceratida and Poecilosclerida. The number of compounds with antibacterial and anti-inflammatory activity was described in 10 papers. Some of the interesting compounds from Indonesian marine sponges are manzamine alkaloids, isolated from sponge of the genus *Acanthostrongylophora*. Manzamine alkaloids have shown their potent activity against infectious and tropical parasitic diseases such as malaria, *Mycobacterium tuberculosis*, *Leishmania* and HIV-1 activities [14].

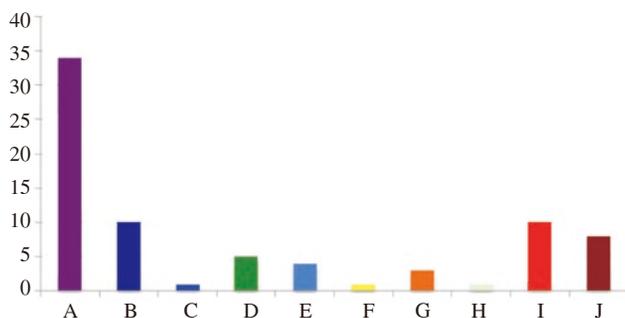


Figure 5. Number of compounds and their biological activities.

A: Anticancer/Cytotoxicity; B: Antibacterial; C: Antituberculosis; D: Antifungal; E: Antimalarial; F: Anti-HIV; G: Anti-viral; H: Anti-Alzheimer's; I: Anti-inflammatory; J: Miscellaneous.

4. Discussion

Unlike terrestrial organisms, marine organisms have to adapt to extreme marine environmental conditions such as high pressure, high salt concentration, low nutrient concentration, low but steady temperature (except the high temperature near underwater volcanoes and the extremely low temperature in polar regions), limited sunlight, and low oxygen content. To acclimatize to these conditions, marine organisms possess unique characteristics that differentiate them from terrestrial organisms [15]. As an archipelagic country, Indonesia is an excellent source of marine organisms that may yield pharmacological activities. The new metabolites from Indonesian marine organisms were mainly isolated from sponges (47 publications) and soft corals (18 publications). Alkaloids, terpenoids, and peptides represented the three main chemical classes of compounds discovered from Indonesian marine organisms, and together with the other chemical classes showed a range of biological activities. Most of the marine natural product studies were conducted by foreign researchers or in collaboration with Indonesian researchers. However, the discovery of new marine natural products by Indonesian researchers is dependent on government support, investment by pharmacological industries, and the expertise of research scientists.

Conflict of interest statement

We declare that we have no conflict of interest.

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