

## POTENTIAL MARINE-DERIVED FUNGI ISOLATED FROM SPONGE IN PRODUCE NEW AND BENEFICIAL COMPOUNDS

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### Abstract

*Marine organisms are a source of natural products and produce compounds with a molecular structure that is unique and useful. Thousands of new compounds have biological activity for anticancer, antiviral, and antimicrobial. This compounds isolated from various marine organism, including from marine-derived fungi. Investigation of chemical compounds from marine-derived fungi isolated from sponge has increased steadily, indicating the important role of marine-derived fungi in the discovery of drug compounds. The sponge has produced various kinds of fungi, which have reported to provide a variety of pharmacologically active metabolites and structurally diverse. Study literature showed that many fungal genera isolated from the marine sponge dominated the genus Acremonium, Aspergillus, Penicillium, Phoma, and Fusarium. The high proportion of genera and new compounds showed that the fungi isolated from the sponge could develop.*

**Keywords :** *Fungi, Marine, Natural Products, Secondary Metabolite*

### INTRODUCTION

Marine organisms have been a rich source of natural products that have a high diversity in the molecular structure and bioactivity (Koenig et al., 2006; and Dewanto et al., 2018; 2019). Marine organisms produce many new compounds with some amazing pharmacological properties (Faulkner, 2000; Mayor and Lehman, 2001; Garcia et al., 2002; Proksch et al., 2002; Amador et al., 2003; Haefner, 2003; Mayer et al., 2003; and Alhaddad et al., 2019). Over the past twenty years, thousands of new compounds and their metabolites with biological activity varied from antiviral, anticancer, antimicrobial have isolated from various marine organism (Faulkner, 2000; Garcia et al., 2002; Amador et al., 2003; Haefner, 2003; and Tanod et al., 2018).

Drug substances from the marine currently hold more than 35 000 samples, with about 150 compounds be cytotoxic to tumor cells (Garcia et al., 2002). Many natural products are efficacious, showed cytotoxic activity, and effective anticancer found in the marine environment

(Wijesekara et al., 2014). Since 1990, there has been increase in the number of pre-clinical anticancer compounds from marine organism that have entered into clinical trials in humans (Lordan et al., 2011).

Investigation of chemical compounds from fungi isolated from marine organism such as algae (Lee et al., 2013), sponge (Proksch et al., 2010) and tunicates (Schmidt et al., 2012) has increased steadily, indicating an important role of marine fungi in the discovery of drug compounds. Fungal organisms become an integral part of life in the biosphere because the fungus has many functional roles in different ecosystems. Obligate marine-derived fungi are fungi that grow and sporulate exclusively in estuarine or marine habitats. Facultative marine-derived fungi are fungi from freshwater or terrestrial habitats are able to grow, and may also sporulate, in the marine environment (Velmurugan et al., 2013). Marine derived fungi are heterotrophic microorganisms that can be found in a variety of substrates as saprophytic and parasitic (Raghukumar, 1990). All groups of fungi including higher

filamentous fungi, yeasts, and fungi thrust chytrids and zoospores, in the form of a saprophyte on detritus as well as parasites on plants and animals in the marine environment. However, a group of fungi varies greatly in different marine ecosystems. There are over 100,000 species of fungi (Blackwell, 2011).

In recent years, there has been evidence that the production of secondary metabolites by the organism is not random, but correlated with ecological niches (Gloer, 1995, 1997). Thus, the chemists trying to isolate microorganisms from unexplored ecological habitats. While macroorganism sea has long been a target for chemical investigation, investigation of marine microorganisms dominated by fungi and bacteria wider attention (Faulkner, 1998). Vasanthabharathi and Jayalakshmi (2013) marine microorganisms have the potential genetic and biochemical diversity of large and become a source of new and effective drugs. Secondary metabolites produced by marine microorganisms are also believed to act as a chemical defense system in the competition for the host (Gallo et al; 2004).

Marine-derived fungus is a rich source of structurally diverse bioactive secondary metabolites with a structure that has never been encountered before and have shown biological activity of a variety of health benefits (Blunt et al., 2006; Smetania et al., 2007). A number of metabolites from marine-derived fungi have antioxidant activity, antimicrobial, anti-tyrosinase or skin lightening, cytotoxic or antitumor, induction of quinone reductase, and anti plasmodial activity. Until recently, many of the structures and pharmacology of bioactive secondary metabolites new and exciting has been isolated from marine-derived fungi. Secondary metabolites produced by marine organisms including marine-derived fungi have a structure that is unique and new (Wijesekara et al., 2014). Marine derived fungi also been reported produce antibacterial compounds (Bugni and Ireland, 2004; Saleem et al., 2007; and Rateb and Ebel, 2011). Marine-derived fungi have been isolated from almost every

marine habitat as possible, including inorganic materials, microbial communities, plants, invertebrates and vertebrates. In particular, the sponge has produced various kinds of fungi, which have been reported to produce a variety of pharmacologically active metabolites and structurally diverse. Marine derived fungi require adaptation and survival in an environment that differs significantly from terrestrial organisms. This may have formed a pattern of their natural products that marine-derived fungi can result in the production of secondary metabolites unique. In this article will discuss the potential of marine-derived fungi were isolated from the sponge as a basic discovery of new compounds is efficacious.

#### **Marine Derived Fungi Secondary Metabolites Isolated From Sponges**

Sponge has been recognized not only as a productive source of bioactive secondary metabolites, but also as a harbor microorganisms such as fungi (Gao et al., 2008). A recent review has shown that of the sponge-derived fungi is the main source for new secondary metabolites (Rateb and Ebel, 2002).

Marine-derived fungi *Gymnascella dankaliensis* isolated from a sponge reported produces two classes of cytotoxic secondary metabolites, polyketides tyrosine and steroid derivatives (Amagata et al., 2013). This fungi isolated from gymnastatin A (1), dankastatin A (2), dankastatin C (3) and demethylcisterol A<sub>3</sub> (4) as can be seen in Figure 1. The compound demethylcisterol A<sub>3</sub> is also produced by the sponge *Homaxinella* (Mansoor et al., 2005 ) from the research dankastatin C is a potential cytotoxic.

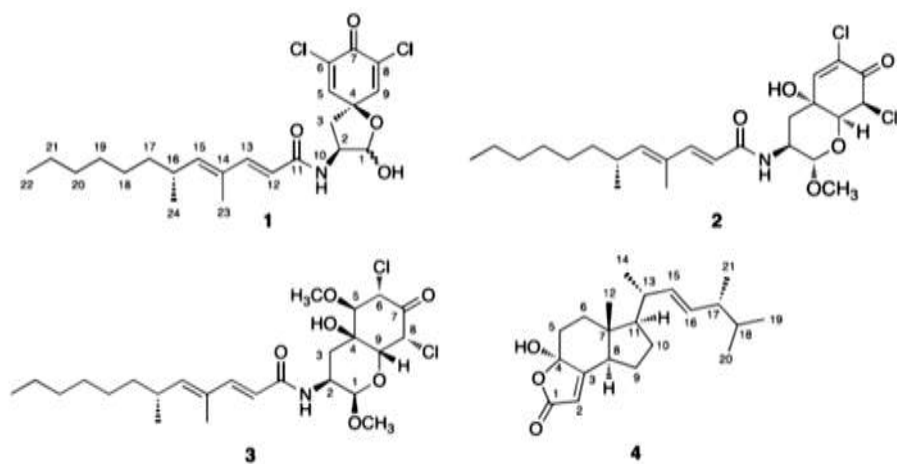


Figure 1. Secondary Metabolites of *Gymnascella dankaliensis*

Metabolite of marine-derived fungi *Penicillium chrysogenum* isolated from the Mediterranean sponge *Ircinia fasciculata* known to produce sorbicillactone A (5),

sorbicillactone B (6) and sorbivinetone (7) (Figure 2) that show anti-leukemia activity (Bringmann et al., 2005).

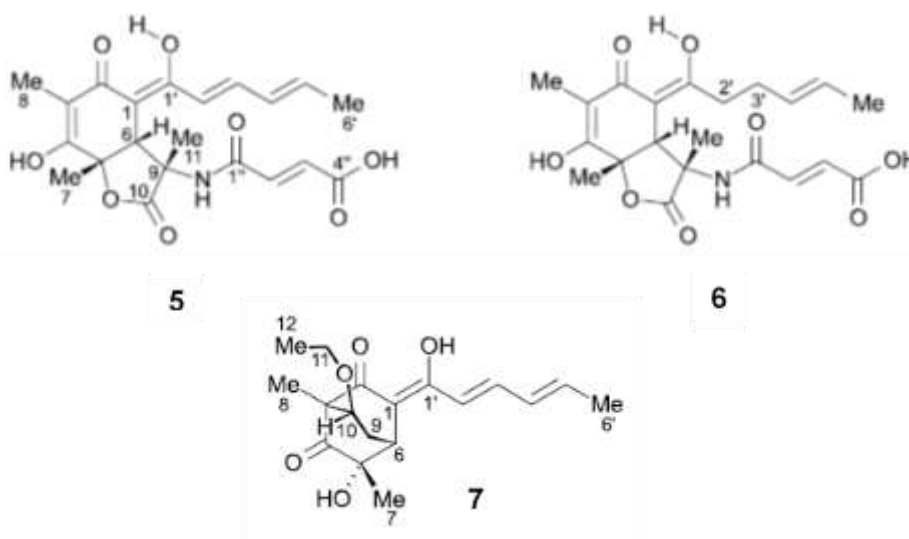


Figure 2. Secondary Metabolites of *Penicillium chrysogenum*

Sesquiterpenoid bisabolane phenolic compounds, disydonols A-C (8-10) (Figure 3), together with (S)-(+)-sydonol (11) compound (Nukina et al., 1981 and Kudo et al., 2009) isolated from marine derived fungi *Aspergillus* sp. of sponge *Xestospongia testudinaria* (Sun et al., 2012). Compounds 8 and 10 showed cytotoxic potential against tumor cell lines.

Sesquiterpenoid bisabolane phenolic compound first isolated from the gorgonian coral *Pseudopterogorgia rigida* (McEnroe and Fenical, 1978). Compounds of this type are also reported to be isolated from the sponge *Didiscus flavus* (Wright et al., 1987), *Didiscus* sp. (Tasdemir et al., 2003), *Epipolasis* sp. (Fusetani et al., 1987) and *Arenochalina* sp. (Butler et al., 1991).

Sesquiterpenoids bisabolane phenolic compounds group also found in marine-derived fungi *Penicillium expansum* (Lu et al., 2010), *Aspergillus sydowi* (Hamasaki et

al., 1978), *Aspergillus* sp. (Nukina et al., 1981 and Wei et al., 2010), *Penicillium* sp. (Henne et al., 1993) and the fungus CNC-979 (Mülhaupt, et al., 2005).

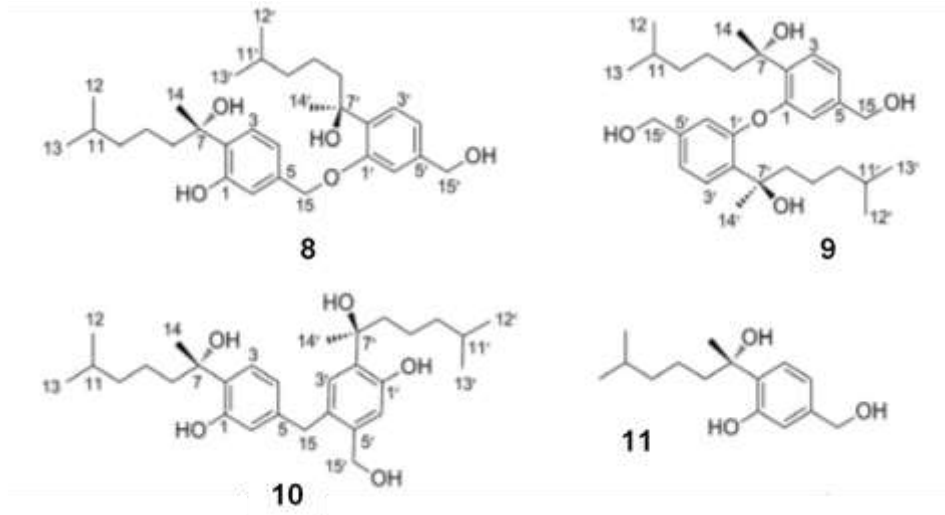


Figure 3. Secondary Metabolites of *Aspergillus* sp.

Four meroterpenoid cytotoxic compounds, tropolactones A-D (12,13,14,15) (Figure 4), which was isolated from the genus marine-derived fungi *Aspergillus* using extract broth (Cueto, MacMillan, Jensen, & Fenical, 2006). This fungus was isolated from a sponge that has not been identified and collected from the Gulf Manele, Hawaii. Meroterpenoid is a compound mixture of terpenes and polyketide biosynthesis, which

has been isolated from plants, microorganisms and invertebrates. In 1970, meroterpenoid compound andibenin B (16) (Dunn et al., 1976) and andilesin A (17) (Dunn et al., 1978) have been isolated from the terrestrial fungi *Aspergillus varicolor*. Isolation tropolactones A-D compound based investigation continues from marine fungi as a source of bioactive metabolites (Bugni and Ireland, 2004; Tan et al., 2004; Rowley et al., 2003; Cueto et al., 2002).

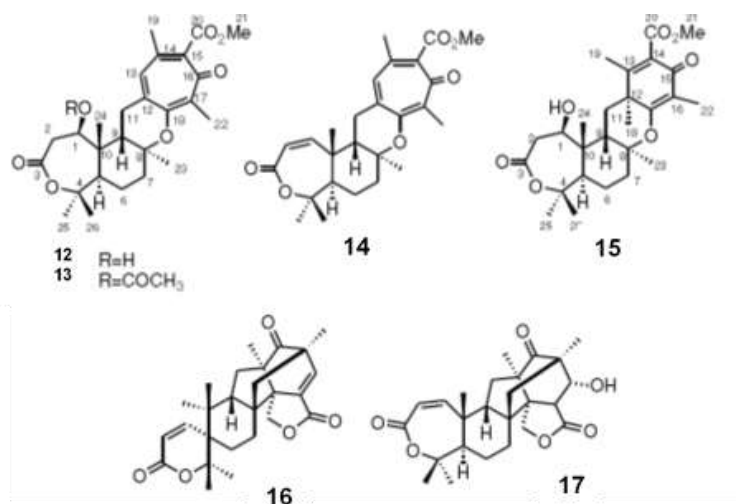


Figure 4. Secondary Metabolites of *Aspergillus*

New diketopiperazine dimer, eurocristatine (18) (Figure 5) isolated from marine-derived fungi *Eurotium cristatum* KUFC 7356 of sponge (Gomes et al., 2012). Species *Eurotium* a sexual state of *Aspergillus* species, especially *Aspergillus glaucus* group (Geiser, 2009). Almeida et al., (2010) reported the ethyl acetate extract *Eurotium cristatum* KUFC 7356 isolated from the sponge showed growth inhibitory activity of three cancer cell lines. Even though some diketopiperazine dimers have been reported previously from a variety of fungal sources, and especially from *Aspergillus* species (Barrow et al., 1993; Barrow and Sedlock., 1994; Cai et al., 2012; Ding et al., 2008; Li et al. 2009; Ovenden et al., 2004; Ruju et al., 2009; Son et al., 1999; Takahashi et al., 1994, 1995a, b; Varoglu et al., 1997; Yamada et al., 2002), eurocristatine a diketopiperazine dimer which was first isolated from the genus *Eurotium*. Eurocristatine structure closely resembles diketopiperazine dimer isolated from marine-derived fungi *Aspergillus niger* (Ovenden et al., 2004). Although eurocristatine not shown cytotoxic activity, antibacterial or antifungal, but eurocristatine a new compound isolated from a group of fungi.

The new compound triprofan is a derivative alkaloid, 3 - ((1-hydroxy-3-(2-methylbut-3-en-2-yl)-2-oxindolin-3-

yl)methyl)-1-methyl-3,4-dihydrobenzo[e][1,4] diazepine-2,5-dione (19), and the new compound meroterpenoid, austalide R (20, 24, 25), as well as three compounds 8-O-4-dehydrodiferulic acid (21) (Bunzel et al., 2003 and Funk et al., 2005), cytochalasin Z17 (22) (Lin et al., 2009), and dihydroisoflavipucin (23) (Loesgen et al., 2011) (Figure 6) are produced by marine-derived fungi *Aspergillus* sp. isolated from the Mediterranean sponge *Tethya aurantium* (Zhou et al., 2014). Cytochalasin Z17 have previously been isolated from *Aspergillus terreus* and *Aspergillus flavus* obtained of *Artemisia annua* and mangrove *Acanthus ilicifolius* (Lin et al., 2009 and Zhang et al., 2010). Dihydroisoflavipucin has also been isolated from *Phoma* sp. of *Salsola oppositifolia* (Loesgen et al., 2011). However, both of these compounds were first reported isolation of fungi isolated from sponge (Zhou et al., 2014). All of these compounds proved to be active against strains of L5178Y murine cancer cells in a cytotoxicity assay. The resulting compound selectively inhibits marine bacterial strains. This is very interesting because it can improve the prospects of produce compounds such as antifouling agents or to fight against epizootics in aquaculture in the future (Zhou et al., 2014).

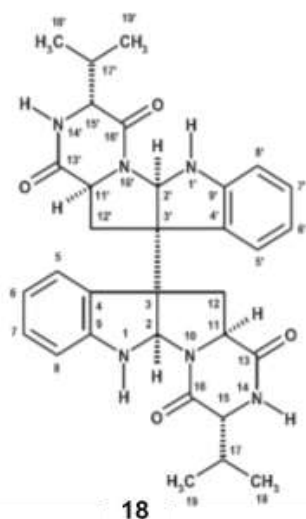


Figure 5. Secondary Metabolites of *Eurotium cristatum* KUFC 7356

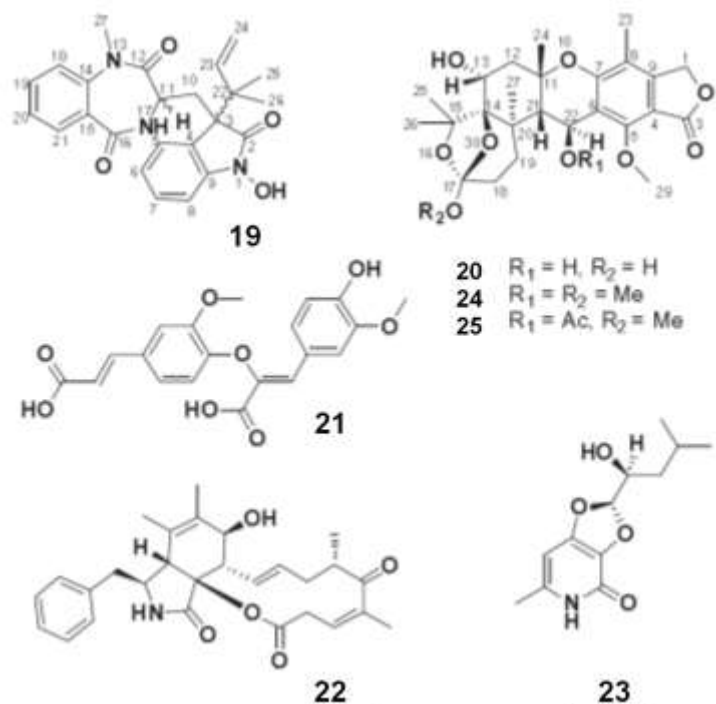


Figure 6. Secondary Metabolites of *Aspergillus* sp

New compounds pentacyclic lactam, diaporthalasin (26), ethyl trihydroxytridecatienoate derivatives, diaporthacol (27), which was isolated as a triacetate derivative (28) (Khamthong, et al., 2014), R-mevalonolactone (29) (Amagata et al., 1998), dothiorelone C (30) (Sommart et al., 2009), (4S, 7S, 13S) -4,7-dihydroxy-1,3-tetradeca-1,5-dienolide (31) (Mancilla et al. 2009), 4b-acetoxy-9b, 10b, 15a-trihydroxyprobotrydial (32) (Collado et al., 1995) and O-methyldihydrobotrydial (33) (Kimura et al., 1988) (Figure 7). The eighth these compounds were isolated from the marine-derived fungi *Diaporthaceae* sp. PSU-SP2 / 4 of the sponge from Pak Meng Beach, Sikao, Trang Province, Thailand (Khamthong et al., 2014). Diaporthalasin showed significant antibacterial activity against *Staphylococcus aureus*.

### Sponge as a Source of Marine Derived Fungi

Marine-derived fungi have been isolated in a variety of substrates such as sediment, algae, mangrove and sponge. More than 40 metabolites of 15 strains of fungi have been isolated (Cheng et al., 1994, Yu et al., 1996, Doshida et al., 1996), are generally included in the genera of terrestrial habitats; eg *Aspergillus* (Abrell, Borgeson & Crews 1996), *Gymnascella* (Numata et al., 1997, Amagata et al., 1998), and *Trichoderma* (Kobayashi et al., 1993). To date, more than 100 metabolites of marine-derived fungi isolated from marine sponges has been reported (Biabani & Laatsch 1998). Some of the metabolites produced has a unique biological activity, such as cytotoxic; eg gymnastatins A-E (Numata et al., 1997, Amagata et al., 1998).

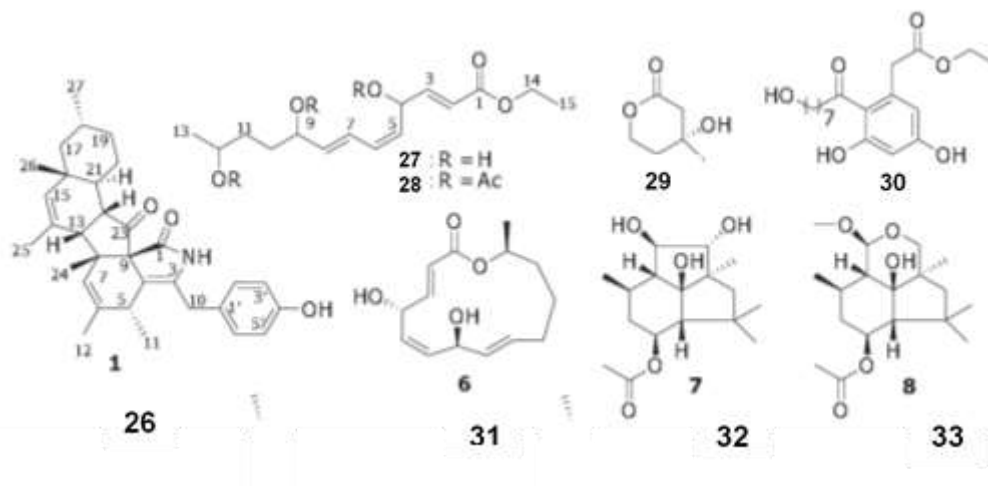


Figure 7. Secondary Metabolites of *Diaporthaceae* sp. PSU-SP2/4

Konig et al., (2000) reported the isolation of different media use only produce quantitative variation in the genus of fungi. 681 fungal strains were isolated from 16 species of sponge and into the 13 genera of Ascomycota, 2 of Zygomycota, and 37 fungi mitosporic; 37 strains remain sterile despite the use of a variety of media and culture conditions to induce sporulation. Fungus genus *Acremonium*, *Aspergillus*, *Penicillium*, *Phoma*, *Fusarium* is the most common genera isolated from the sponge. Krohn et al., 1992, 1994a, b also reported that the genus *Acremonium*, *Aspergillus*, *Penicillium*, *Fusarium* is a genus of the most frequently isolated from marine organisms.

Various methods have been carried out to isolate microorganisms from the marine environment, particularly sponge (Schulz et al., 1993). Isolation method performed on the surface of the sponge, so that the fungus isolated nature can not be determined whether mutualistic symbionts, parasites, or derived from the environment and is present by chance (Konig et al., 2000). Most marine-derived fungi isolates were isolated from the sponge of the terrestrial habitats genera (Roth, Orpurt & Ahearn, 1964; Schaumann, 1974; Miller & Whitney, 1981). Nevertheless unique secondary metabolites produced depends on the characteristics of each habitat (Kobayashi et al., 1993; Yu et al., 1996; Numata et al., 1997).

Konig et al., (2000) reported that 81.5% of the 92 fungal culture extracts were isolated from the sponge showed a relatively high proportion produce antimicrobial metabolites. Some fungal isolates from sponge also produces metabolites active against *Mycobacterium tuberculosis* and HIV-1 reverse transcriptase (RT) and tyrosine kinase (TK), an enzyme important target for the treatment of AIDS and cancer (Bolen and Brugge, 1997; Mitsuya and Broder, 1987). Fungi were isolated from the sponge is important as a source of new metabolites for pharmaceutical and agrochemical industries, all compounds isolated from the extracts, tested and biologically active. Moreover, the resulting compounds are generally new compounds with unique structures (Holler et al., 1999 a, b).

Based on the above description then, marine-derived fungi were isolated from the sponge is a competitive source for new natural products are biologically active. The high proportion of genera and new compounds showed that the fungus isolated from the sponge can be developed. As shown by Schulz et al., (1996, 1999a, b), the ecological niche plays an important role in the spread of the fungi. The new method of isolation should also be developed to selectively isolate marine-derived fungi from sponge, as it is likely that only a small portion of the fungi was isolated using conventional methods (Hawksworth, 1991).

Marine derived fungi produces a higher proportion of new secondary metabolites such as those found fungi from the other extreme habitats (Dreyfuss, 1986 and Schulz et al., 1999b).

## CONCLUSION

Marine-derived fungi are potential organisms to produce compounds with the unique structure and biological activity. Sponge is one organism that is the source of isolation of marine-derived fungi. The number of marine-derived fungi isolated from the sponge may differ in a number. In addition, the production of secondary metabolites produced by fungi depends on ecological niches. Secondary metabolites isolated from marine-derived fungi can be different even from the same host. This indicates that the isolation of compounds from marine-derived fungi is an opportunity to discover new compounds with unique and useful molecular structure.

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