Marine Sponge-Derived Fungi: Fermentation and Cytotoxic Activity

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ABSTRACT
Bioactive compounds from sponges are produced under the influence of several factors including enzymes, nutrients, and the result of symbiosis with other microbes like fungi. Marine sponge-derived fungi are a potential source producing new bioactive compounds for future cancer therapies. In this review, we summarize 132 components consisting of 16 extracts, 5 fractions, and 111 isolates obtained from 30 genera of marine sponge-derived fungi tested on 317 types of cell line cancers from articles published through June 2020. These components were classified as very strong, strong, and moderate cytotoxic activity based on their IC50 respectively, and 56 components of marine sponge-derived fungi were reported as very strong cytotoxic activity. Components that have very strong cytotoxic activity have been summarized, including polyketide derivatives, lipopeptides, cyclodepsipeptides, decalin derivatives, xanthone derivatives, phenol derivatives, cytochalasins, peptaibiotics, phthalides, anthraquinones, terpenes, decalin derivatives, and lactones. In producing bioactive metabolites for cytotoxic, the fermentation media play an important role. Carbon sources, nitrogen, salinity, and extracted specimens are important factors in the production of bioactive metabolites for cytotoxic from marine sponge-derived fungi. With this up-to-date review, we attempt to present new minding in the rational discovery of lead compounds for the development of cancer therapy.

INTRODUCTION
The association between sponges and sponge symbionts has potential in drug discovery. Not only are secondary metabolites produced by sponges, but also sponge symbionts may synthesize secondary metabolites. Therefore, the microbial symbionts associated with sponges can be isolated and cultured to increase the production of certain bioactive compounds derived from sponges (Lee et al., 2001). Marine sponge-derived fungi are a source of secondary metabolites that are currently being studied intensively. Although research on fungi derived from marine sponges is still less than research on terrestrial fungi, several important findings derived from fungi associated with marine sponges have added to the value of these fungi in the discovery of natural products (Butler et al., 2014), such as various kinds of secondary metabolites which have antimarial, antiviral, antibacterial, and anticancer or cytotoxic activity. It is a potential that should be explored to increase the number of medicines derived from marine life without damaging the marine biota itself (Debbab et al., 2011; Hikmawan et al., 2020; Huang et al., 2011).

The metabolites produced by fungi coming from marine sponges are the result of chemical communication between fungus and sponge which is mutually beneficial; moreover, in some cases, they can produce completely new metabolites (Pejin and Karaman, 2017). The symbiosis between fungi and sponges, among others, provides a source of nutrition, a place of defense and protection, and stabilization of the sponge structure, treats sponge waste, and produces bioactive compounds. Therefore, it is likely that the bioactive compounds are also produced by the associated fungi of these sponges (Proksch et al., 2002; Thomas et al., 2010). Data obtained from the National Cancer Institutes of the United States show that sponges are a potential source of compounds in producing cytotoxic effects (Brinkmann et al.,...
Thus, marine sponge-derived fungi also have the potential to produce bioactive compounds as cytotoxic.

To produce bioactive compounds, the associated fungi derived from marine sponges must be fermented outside the sponge’s body tissue using a fermentation media. The fermentation of microorganisms in this case is a fungus which will be influenced by physical and chemical factors. Physical factors affecting microorganisms comprise temperature, pH, and osmotic salinity, while chemical factors consist of sources of carbon, nitrogen, and nutrients in culture media (Pratiwi, 2008). The marine sponge-derived fungi depend on carbon, nitrogen, and salt (salinity) sources. Fungi associated with the marine environment based on several studies are strongly influenced by their growth in the presence of simple carbon sources, such as glucose and dextrose, and can even affect the production of secondary metabolites that affect their biological activity (Anuhya et al., 2017; Fuentes et al., 2015; Mahapatra et al., 2013; Miller et al., 1981; Ripa et al., 2009; Sguros and Simms, 1963). The increase in salt content (salinity) beyond seawater causes several species of associated fungi from the sea to decrease their growth rate, but the unavailability of salinity inhibits the growth of these associated fungi from the sea (Amon and Yei, 1982; Huang et al., 2011; Jones, 2000; Venkatachalam et al., 2019).

The objective of this review is to summarize the components extracted from the fermentation of marine sponge-derived fungi which have cytotoxic activity, identify the potential cytotoxic activity of these components based on the IC₅₀ value, and find out what influences the fermentation conditions from marine sponge-derived fungi to produce cytotoxic bioactive compounds. The advantage of this review is to determine the relationship between the cytotoxic activity of fungi derived from marine sponges and their fermentation medium in producing cytotoxic compounds which have the potential to be developed as future cancer drug candidates. In the future, this review can be used as a reference to produce potential cytotoxic compounds from fungi from marine sponges using optimal fermentation medium conditions.

METHOD

A systematic search was conducted to find all publications related to the topic up to June 2020 on PubMed and Google Scholar. The keywords used to browse the articles were “fungi, sponge-derived, cytotoxic” or “fungi, sponge-associated, cancer”. The data included in this review were primary articles in English regarding cytotoxic studies of components produced from fungi derived from marine sponges and the conditions of fermentation, as shown in Table 1. Articles were excluded from primary articles if they were review articles, conference articles, and thesis, and no data were available for retrieval. All synthetic derivatives of natural metabolites that occur in sponges are not mentioned in this review. The variables assessed in this review include sponge species/genera of sponges, fungi-associated species/genera, fermentation medium, extracted specimens from fermentation products, components of the extracted product, type of cancer, type of cell line, and the cytotoxic effect of these components.

Cytotoxic activity of marine sponge-derived fungi

The number of articles that has been searched to June 2020 was 86 primary articles (Table 1). We identified that the 30 genera of sponge and 30 genera of fungi derived from the sponge investigated were related to their cytotoxic activity. The genera of sponges that are most frequently studied are Calliypsongia, Halichondria, Phakellia, and Petrosia. The most frequently studied sponge-derived fungal genera are Aspergillus, Penicillium, Trichoderma, and Gymnascella. Figure 1 shows the number of studies that have been conducted for the cytotoxic activity of marine sponge-derived fungi, of which the number of publications is increasing from year to year. The highest number of publications published in 2019 was 14 articles, followed by 2018 and 2017 with 12 and 11 articles, respectively. The number of publications from 1997 to 2016 continued to increase, but the number of articles per year has not exceeded 2017–2019. It indicates that the focus of research in 1997–2016 was still on marine sponges explored for their bioactive components. Excessive exploration causes damage to the ecosystem of the sponge, which made the species decrease, and is not balanced with sponge growth. It creates a new trend, in which many scientists are interested in researching endophytic samples from sponges, including endophytic fungi from sponges, and it absolutely reduces the damage to sponge the habitat, which is increasingly rare in nature (Carroll et al., 2019; Thomas et al., 2010). Secondary metabolites from sea sponges have also been studied and have the potential in the medical world, including antiviral, antimutant, antimicrobial, antimalarial, and cytotoxicity (Guo et al., 2019; Hikmawan et al., 2020; Setyowati et al., 2009; Wang, 2006). Several studies have reported that the bioactive compounds obtained from sea sponges are most likely secondary metabolite compounds produced by the associated microbes in the bodies of marine sponges. It is caused by 40%–50% of the body tissue of marine sponges, which consists of microbes (Proksch et al., 2002; Thakur and Müller, 2004). The marine sponge association microbes can be fungi (Thomas et al., 2010).

Marine sponge-derived fungi produce bioactive compounds depending on the surrounding environment. The original habitat of these fungi is symbiotic in sponge tissues; thus, the production of compounds depends on the results of symbiosis with the host. When this fungus is outside its host, the active compound produced depends on the medium growth for the fungus. To be able to produce bioactive compounds similar to those produced in symbiosis with a sponge, the growth medium is made as closely as possible to the situation in its host. In addition to obtaining active compounds, it is also to reduce the occurrence of mutations that occur in fungi (Debbab et al., 2011; Huang et al., 2011; Kjer et al., 2010; Lee et al., 2001). Research on cytotoxic agents derived from marine sponges and their symbiotic microbes is still the concern of natural product researchers. More than 10% of cytotoxic activity comes from marine sponges that have been identified to date. The symbiosis of microorganisms from sponsors is proven to have an important role in bioactive compounds as cytotoxic agents. A review from 1955 to 2016 of marine sponges acting as cytotoxic agents reported that 107 new cytotoxic agents originated from marine sponges and were thought to have originated in symbiosis with the microbes present in these sponges (Zhang et al., 2017).
Table 1. Summarized data of fermentation condition and cytotoxic activity from marine sponge-derived fungi.

| No. | Sponge species                     | Fungi association          | Fermentation medium | Extraction specimen | Compound | Cancer type                  | Cell line | IC_{50} (µg/ml) | Ref.                      |
|-----|-----------------------------------|----------------------------|---------------------|---------------------|----------|----------------------------|-----------|----------------|---------------------|
| 1   | Halichondria japonica             | Gymnascella dankanliensis  | Malt, glucose, peptone, and artificial seawater | Mycelia             | Gymnastatin A | Mouse leukemia              | P338      | 18.00          | (Numata et al., 1997) |
|     |                                   |                            |                     |                     | Gymnastatin B |                                           |           | 108.00         |                      |
|     |                                   |                            |                     |                     | Gymnastatin C |                                           |           | 106.00         |                      |
| 2   | H. okadai                         | T. harzianum               | Glucose, peptone, malt, and artificial seawater | Medium              | Trichodenone A | Mouse leukemia              | P338      | 0.21           | (Amagata, et al., 1998b) |
|     |                                   | OUPS-N 115                 |                     |                     | Trichodenone B |                                           |           | 1.21           |                      |
|     |                                   |                            |                     |                     | Trichodenone C |                                           |           | 1.45           |                      |
|     |                                   |                            |                     |                     | Harzialactone B |                                           |           | 60.00          |                      |
| 3   | Halichondria japonica             | G. dankanliensis           | Malt, glucose, peptone, and artificial seawater | Mycelia             | Gymnasterones A | Mouse leukemia              | P338      | 10.10          | (Amagata, et al., 1998a) |
|     |                                   |                            |                     |                     | Gymnasterones B |                                           |           | 1.60           |                      |
| 4   | Halichondria japonica             | G. dankanliensis           | Malt, glucose, peptone, and artificial seawater | Mycelia             | Dankasterone   | Mouse leukemia              | P338      | 2.20           | (Amagata et al., 1999) |
| 5   | Zyzya sp.                         | Penicillium brocae         | Sucrose, salt (NaNO₃, KH₂PO₄, MgSO₄, KCl, FeSO₄), and water | Mycelia and medium  | Brocaenol A   | Human colon cancer          | HCT-116   | 20.00          | (Bugni et al., 2003) |
|     |                                   |                            |                     |                     | Brocaenol B   |                                           |           | 50.00          |                      |
|     |                                   |                            |                     |                     | Brocaenol C   |                                           |           | > 50.00        |                      |
| 6   | Axinella damicornis Esper          | Aspergillus niger          | Glucose, soya peptone, malt extract, yeast extract, sea salt, and water | Mycelia and medium  | Bicoumanigrin A| Human leukemia               | Jurassic  | > 20.00        | (Hiort et al., 2004) |
|     |                                   |                            |                     |                     |                       | Human lymphoma              | U937      | > 20.00        |                      |
|     |                                   |                            |                     |                     |                       | Human leukemia              | MV4-11    | > 20.00        |                      |
|     |                                   |                            |                     |                     |                       | Human leukemia              | NB-4      | > 20.00        |                      |
| 7   | Halichondria japonica             | G. dankanliensis           | Malt, glucose, peptone, and artificial seawater | Mycelia             | Gymnastatin F | Mouse leukemia              | P338      | 0.13           | (Amagata et al., 2006) |
|     |                                   |                            |                     |                     | Gymnastatin G |                                           |           | 0.03           |                      |
| 8   | Teichaxinella sp.                 | Acremonium sp.             | Sucrose, salt (NaNO₃, K₂PO₄, MgSO₄, KCl, MgCl₂, FeSO₄), and seawater | Medium              | Efrapeptin G | Human colon cancer          | HCT-116   | 0.01           | (Boot et al., 2006)  |
| 9   | Unidentified marine sponge        | Clonostachys sp. E5NA-A009 | Glucose, beef extract, yeast extract, starch, tryptone, NaCl, KCl, MgCl₂, and water | Mycelia             | IB-01212 | Human prostate cancer       | LN-capP   | 0.01           | (Cruz et al., 2006)  |
|     |                                   |                            |                     |                     |                       | Human breast cancer         | SK-BR3    | 0.01           |                      |
|     |                                   |                            |                     |                     |                       | Human colon cancer          | HT-29     | 0.01           |                      |
|     |                                   |                            |                     |                     |                       | Human cervix cancer         | HeLa      | 0.01           |                      |
| 10  | Unidentified marine sponge        | Aspergillus sp.            | Mannitol, hydrolyzed fish soluble, Menhaden meal, kelp powder, and seawater | Mycelia             | Tropolactones A | Human colon cancer          | HCT-116   | 13.20          | (Cueto et al., 2006) |
|     |                                   |                            |                     |                     | Tropolactones B |                                           |           | 10.90          |                      |
|     |                                   |                            |                     |                     | Tropolactones C |                                           |           | 13.90          |                      |
| 11  | Halichondria japonica             | G. dankanliensis           | Media A: malt extract, soluble starch, peptone, artificial seawater | Mycelia             | Dankasterones A (from media A) | Mouse leukemia | P338 | 2.20          | (Amagata et al., 2007) |
|     |                                   |                            |                     |                     | Dankasterones B (from media A) |               |     | 2.80           |                      |
|     |                                   |                            |                     | Media B: malt extract, glucose, peptone, and artificial seawater | Gymnasterones A | Mouse leukemia | P338 | 10.10          |                      |
|     |                                   |                            |                     |                     | (from media B) |                                           |           |                      |
|     |                                   |                            |                     |                     | Gymnasterones B (from media B) | | | | |
|     |                                   |                            |                     |                     | Gymnasterones C (from media B) | | | | |
|     |                                   |                            |                     |                     | Gymnasterones D (from media B) | | | | |
| 12  | Mycale plumose                    | Penicillium aurantiogriseum | Sorbitol, maltose, glutamine, KH₂PO₄, MgSO₄, tryptophan, yeast extract, and seawater | Medium              | Aurantiomide B | Mouse leukemia              | P338      | 54.00          | (Xin et al., 2007)  |
|     |                                   |                            |                     |                     |                       | Human leukemia              | HL-60     | 52.00          |                      |
|     |                                   |                            |                     |                     |                       | Mouse leukemia              | P338      | 48.00          |                      |
|     |                                   |                            |                     |                     |                       | Human liver cancer          | BEL-7402  | 62.00          |                      |
| 13  | Unidentified marine sponge        | Aspergillus ostianus strain | Potato, dextrose, bromine, and water | Medium              | Aspergilides A | Mouse leukemia              | L1210     | 2.10           | (Kito et al., 2008)  |
|     |                                   | 01F313                     |                     |                     | Aspergilides B |                                           |           | 71.00          |                      |
|     |                                   |                            |                     |                     | Aspergilides C |                                           |           | 2.00           |                      |
| No. | Sponge species | Fungi species | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC\(_{50}\) (µg/ml) | Ref. |
|-----|----------------|---------------|---------------------|--------------------|----------|-------------|-----------|----------------|------|
| 14  | *Suberites domuncula* | *Aspergillus ustus* | Barley, spelt whole grain flakes, soy peptone, MnCl\(_2\), water | Mycelia and medium | Ophiobolin H | Mouse lymphoma | L5178Y | 1.90 | (Proksch et al., 2008) |
| 15  | *Tethya aurantium* | *Scopulariopsis brevicadis* strain NCPF 2177 | Glucose, soya peptone, malt extract, yeast extract, NaCl, and water | Mycelia | Scopularides A | Human pancreatic cancer | COLO 357 | > 10.00 | (Yu et al., 2008) |
| 16  | *Petrosia sp.* | *Paecilomyces lilacinus* | Malt extract, D-glucose, peptone, and seawater | Mycelia and medium | Phomaligol A | Human lung cancer | A-549 | n.a. | (Elbandy et al., 2009) |
|     |                |              |                     |                    |          | Human ovarian cancer | SK-OV-3 | n.a. |              |
|     |                |              |                     |                    |          | Human skin cancer | SK-MEL-2 | n.a. |              |
|     |                |              |                     |                    |          | Human CNS cancer | XF-498 | n.a. |              |
|     |                |              |                     |                    |          | Human colon cancer | HCT-15 | n.a. |              |
| 17  | *Suberites domuncula* | *A. ustus* | Barley, spelt whole grain flakes, soy peptone, MnCl\(_2\), and water | Mycelia and medium | Ester of (E,E)-6-oxo-2,4-hexadienoic acid | Mouse lymphoma | L5178Y | 0.60 | (Liu et al., 2009) |
|     |                |              |                     |                    |          | Mouse pheochromocytoma | PC-12 | 7.20 |              |
|     |                |              |                     |                    |          | Human cervix cancer | HeLa | 5.90 |              |
| 18  | *E. perox* | *Phoma sp.* | Biomalt and artificial seawater | Mycelia and medium | Epoxysphomalin A | Human bladder cancer | BXF 1218 L | 0.02 | (Mohamed et al., 2009) |
|     |                |              |                     |                    |          | Human glioblastoma | CNXF 498NL | 0.02 |              |
|     |                |              |                     |                    |          | Human colon cancer | SF-268 | 0.35 |              |
|     |                |              |                     |                    |          |                  | HCT-116 | 0.33 |              |
|     |                |              |                     |                    |          |                  |                  | 0.20 |              |
|     |                |              |                     |                    |          | Human gastric cancer | GXF 251 L | 0.03 |              |
|     |                |              |                     |                    |          | Human lung cancer | LXF 1121 L | 0.38 |              |
|     |                |              |                     |                    |          | Human lung cancer | LXF 289 L | 0.43 |              |
|     |                |              |                     |                    |          | Human lung cancer | LXF 526 L | 0.43 |              |
|     |                |              |                     |                    |          | Human lung cancer | LXF 529 L | 0.08 |              |
|     |                |              |                     |                    |          | Human lung cancer | LXF 629 L | 0.04 |              |
|     |                |              |                     |                    |          | Human colon cancer | NCI-H460 | 0.31 |              |
|     |                |              |                     |                    |          | Human breast cancer | MAXF 401NL | 0.01 |              |
|     |                |              |                     |                    |          | Human skin cancer | MEXF 276 L | 0.05 |              |
|     |                |              |                     |                    |          | Human skin cancer | MEXF 394NL | 0.28 |              |
|     |                |              |                     |                    |          | Human skin cancer | MEXF 462NL | 0.06 |              |
|     |                |              |                     |                    |          | Human skin cancer | MEXF 514 L | 0.38 |              |
|     |                |              |                     |                    |          | Human skin cancer | MEXF 520 L | 0.32 |              |
|     |                |              |                     |                    |          | Human ovarian cancer | OVFX 1619 L | 0.26 |              |
|     |                |              |                     |                    |          | Human ovarian cancer | OVFX 899 L | 0.08 |              |
|     |                |              |                     |                    |          | Human ovarian cancer | OVFX OVCAR3 | 0.02 |              |
|     |                |              |                     |                    |          | Human pancreatic cancer | PAXF 1657 L | 0.03 |              |
|     |                |              |                     |                    |          | Human prostate cancer | PANCl | 0.33 |              |
|     |                |              |                     |                    |          | Human prostate cancer | PRXF 22RV1 | 0.03 |              |
|     |                |              |                     |                    |          | Human mesothelioma | DX145 | 0.75 |              |
|     |                |              |                     |                    |          | Human mesothelioma | LN-encap | 0.94 |              |
|     |                |              |                     |                    |          | Human mesothelioma | PXF 1752 L | 0.03 |              |
|     |                |              |                     |                    |          | Human kidney cancer | RXF 1781 L | 0.47 |              |
| No. | Sponge species | Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC<sub>50</sub> (µg/ml) | Ref. |
|-----|---------------|------------------|--------------------|-------------------|----------|-------------|-----------|------------------|------|
| 19  | *Petrosia* sp. | *A. vernicolor*   | Malt extract, glucose, peptone, and seawater | Mycelia and medium | Fellutamide C | Human uterus cancer | RXF 393NL | 0.08             |      |
|     |               |                  |                    |                   |          | Human lung cancer | RXF 486 L | 0.03             |      |
|     |               |                  |                    |                   |          | Human ovarian cancer | RXF 944 L | 0.32             |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  | 13.26            | (Lee, et al., 2010a) |
|     |               |                  |                    |                   |          | Human CNS cancer |                  | 2.84             |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  | 2.17             |      |
| 20  | *Petrosia* sp. | *A. vernicolor*   | Malt extract, glucose, peptone, and seawater | Mycelia and medium | Methyl averantin | Human lung cancer |                  | 0.64             | (Lee, et al., 2010b) |
|     |               |                  |                    |                   |          | Human ovarian cancer |                  | 1.17             |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  | 1.10             |      |
|     |               |                  |                    |                   |          | Human CNS cancer |                  | 0.41             |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  | 1.73             |      |
| 21  | *Pseudoceratina purpurea* | *Trichirachium sp.* | Brown rice, yeast extract, Na-tartrate, KH<sub>2</sub>PO<sub>4</sub>, and water | Mycelia and medium | JBIR-97 | Human cervix cancer |                  | 6.78             | (Ueda et al., 2010) |
|     |               |                  |                    |                   |          | Human mesothelioma |                  | 19.10            |      |
|     |               |                  |                    |                   |          | Human cervix cancer |                  | 10.47            |      |
|     |               |                  |                    |                   |          | Human mesothelioma |                  | 38.82            |      |
|     |               |                  |                    |                   |          | Human mesothelioma |                  | 10.47            |      |
|     |               |                  |                    |                   |          | Human lung cancer |                  | 36.35            |      |
|     |               |                  |                    |                   |          | Human breast cancer |                  | 10.23            | (Almeida et al., 2011) |
|     |               |                  |                    |                   |          | Human globloblastoma |                  | 6.60             |      |
|     |               |                  |                    |                   |          | Human leukemia |                  | 9.54             |      |
| 22  | *Callyspongia* sp. | cf. C. flammae | Stachylidium sp. | Biomalt, sea salt, and water | Mycelia and medium | Marilones C | Human cervix cancer |                  | 5.00 x 10<sup>4</sup> | (Cohen et al., 2011) |
|     |               |                  |                    |                   |          | Human mesothelioma |                  | 10.19            | (Ehada et al., 2011) |
|     |               |                  |                    |                   |          | Human cervix cancer |                  | 1.19             |      |
|     |               |                  |                    |                   |          | Human ovation cancer |                  | 7.13             |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  | 1.20             |      |
|     |               |                  |                    |                   |          | Human CNS cancer |                  | 0.67             |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  | 0.14             |      |
|     |               |                  |                    |                   |          | Human lung cancer |                  | 0.13             |      |
| 23  | *Psammocinia* sp. | *Aspergillus* insuetus | Potato, dextrose, and water | Medium | Insuetolide C | Human leukemia |                  |                  |      |
|     |               |                  |                    |                   |          | Mouse lymphoma |                  |                  |      |
|     |               |                  |                    |                   |          | Human ovation cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human ovation cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human CNS cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human lung cancer |                  |                  |      |
| 24  | *G. cydionium* | *Arthrinium* sp. | Barley, spelt whole grain flakes, soy peptone, MnCl<sub>2</sub>, and water | Mycelia and medium | Anomalalin A | Mouse lymphoma |                  |                  |      |
|     |               |                  |                    |                   |          | Human ovation cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human ovation cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human CNS cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human lung cancer |                  |                  |      |
| 25  | *Petrosia* sp. | *A. versicolor*   | Malt extract, glucose, peptone, and seawater | Mycelia and medium | Fellutamide F | Human cervix cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human mesothelioma |                  |                  |      |
|     |               |                  |                    |                   |          | Human cervix cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human mesothelioma |                  |                  |      |
|     |               |                  |                    |                   |          | Human lung cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human ovarian cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human CNS cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  |                  |      |
| 26  | *Stelletta* sp. | *Penicillium* sp. (J05B-3-F-1) | Malt extract, glucose, peptone, and seawater | Mycelia and medium | (3S)-Hexylitaconic acid | Mouse lymphoma |                  |                  |      |
|     |               |                  |                    |                   |          | Human ovation cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human skin cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human CNS cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human colon cancer |                  |                  |      |
| 27  | *Suberites domuncula* | *A. ustus* strain | Barley, spelt whole grain flakes, soy peptone, MnCl<sub>2</sub>, and water | Mycelia and medium | Aspergillamide A | Mouse lymphoma |                  |                  |      |
|     |               |                  |                    |                   |          | Aspergillamide B |                  |                  |      |
| 28  | *Xestospongia testudinaria* | *Aspergillus* sp. | Glucose, yeast extract, peptone, and seawater | Medium | Aspergiterpenoid A | Human cervix cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human liver cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human liver cancer |                  |                  |      |
| 29  | *Xestospongia testudinaria* | *Aspergillus* sp. | Glucose, yeast extract, peptone, and seawater | Medium | Disydonol A | Human cervix cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human liver cancer |                  |                  |      |
|     |               |                  |                    |                   |          | Human liver cancer |                  |                  |      |
| No. | Sponge species & Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC<sub>50</sub> (µg/ml) | Ref. |
|-----|-----------------------------------|---------------------|---------------------|----------|------------|----------|----------------------|------|
| 30  | Unidentified marine sponge CR6242 & Aspergillus unguis CR1282-03 | Potato, dextrose, and seawater | Medium | Aspergillusidone C | Human bile duct cancer | HuCCA-1 | 22.97 | (Sureram et al., 2012) |
|     |                                   |                     |                     |          |            |          |                      |      |
|     |                                   |                     |                     |          | Human liver cancer | HepG-2 | 32.00 |                  |      |
|     |                                   |                     |                     |          | Human lung cancer | A-549 | 22.97 |                  |      |
|     |                                   |                     |                     |          | Human leukemia | MOLT-3 | 12.96 |                  |      |
|     |                                   |                     |                     |          | Human leukemia | MOLT-3 | 4.17 |                  |      |
| 31  | Homaxinella sp. & G. dankaliensis | Malt extract, soluble starch, peptone, and artificial seawater | Mycelia | Gymnastatin A | Mouse leukemia | P338 | 0.02 | (Amagata et al., 2013) |      |
|     |                                   |                     |                     |          | Dankastatin C |        | 0.06 |                  |      |
| 32  | Unidentified marine sponge & Stachybotry sp. HH1 ZDDS1F1-2 | Rice, sea salt, and water | Mycelia and medium | Grisephenone A | Human lymphoma | U937 | 7.92 | (Qin et al., 2014) |      |
|     |                                   |                     |                     |          | Human cervix cancer | HeLa | 5.14 |                  |      |
| 33  | Hymeniacidon perleve & A. versicolor Hmp-F48 | Potato, sucrose, and water | Mycelia and medium | 4,6-Dimethoxy-2,9-dimethylphenol[b.e] [1,4]dioxine-1,7-diol | Human leukemia | HL-60 | 1.10 | (Wang et al., 2014) |      |
| 34  | Niphates sp. & Hansfordia sinuosae | Rice and water | Mycelia and medium | Punctaporonin H | Human colon cancer | HCT-8 | > 3.10 | (Wu et al., 2014) |      |
|     |                                   |                     |                     |          | Human liver cancer | BEL-7402 | > 3.10 |                  |      |
|     |                                   |                     |                     |          | Human gastric cancer | BGC-823 | > 3.10 |                  |      |
|     |                                   |                     |                     |          | Human lung cancer | A-549 | > 3.10 |                  |      |
|     |                                   |                     |                     |          | Human ovarian cancer | A2780 | > 3.10 |                  |      |
| 35  | H. okadai & T. harzianum OUPS-111D-4 | Glucose, malt extract, peptone, and artificial seawater | Medium | Tandyukisin | Mouse leukemia | P338 | 25.19 | (Yamada et al., 2014) |      |
|     |                                   |                     |                     |          | Human leukemia | HL-60 | 19.51 |                  |      |
|     |                                   |                     |                     |          | Mouse leukemia | L1210 | 19.09 |                  |      |
|     |                                   |                     |                     |          | Trichoharzin | P338 | 10.13 |                  |      |
|     |                                   |                     |                     |          | Human leukemia | HL-60 | 6.66 |                  |      |
|     |                                   |                     |                     |          | Mouse leukemia | L1210 | 10.53 |                  |      |
| 36  | P. fusca & A. arundinis ZSDS1-F3 | Sorbitol, maltose, yeast extract, MSG, KH<sub>2</sub>PO<sub>4</sub>, MgSO<sub>4</sub>, and water | Mycelia and medium | Cytochalasin K | Human leukemia | K562 | 5.20 | (Wang et al., 2015) |      |
|     |                                   |                     |                     |          | Human lung cancer | A-549 | 6.78 |                  |      |
|     |                                   |                     |                     |          | Human liver cancer | Hub-7 | 5.40 |                  |      |
|     |                                   |                     |                     |          | Human lung cancer | H1975 | 9.46 |                  |      |
|     |                                   |                     |                     |          | Human breast cancer | MCF-7 | > 24.76 |                  |      |
|     |                                   |                     |                     |          | Human lymphoma | U937 | > 24.76 |                  |      |
|     |                                   |                     |                     |          | Human gastric cancer | BGC-823 | > 24.76 |                  |      |
|     |                                   |                     |                     |          | Human leukemia | HL-60 | 5.50 |                  |      |
|     |                                   |                     |                     |          | Human cervix cancer | HeLa | 23.47 |                  |      |
|     |                                   |                     |                     |          | Human leukemia | MOLT-4 | 5.84 |                  |      |
| 37  | Cinachyrella sp. & E. variecolor | Potato, dextrose, and water | Mycelia and medium | Varioxiranol K | Human colon cancer | HCT-116 | 1.44 | (Wu et al., 2015) |      |
|     |                                   |                     |                     |          | Human liver cancer | HeLa | 2.65 |                  |      |
|     |                                   |                     |                     |          | Human liver cancer | HepG-2 | 3.65 |                  |      |
|     |                                   |                     |                     |          | Human lung cancer | BGC-823 | 1.76 |                  |      |
|     |                                   |                     |                     |          | Human ovarian cancer | A2780 | 1.18 |                  |      |
| 38  | Unidentified Marine Sponge & Alternaria sp. SP-32 | Sorbitol, maltose, MSG, KH<sub>2</sub>PO<sub>4</sub>, MgSO<sub>4</sub>, tryptophane, yeast extract, sea salt, and water | Medium | AS2-1 | Human cervix cancer | HeLa | 167.00 | (Chen et al., 2016) |      |
|     |                                   |                     |                     |          | Human leukemia | HL-60 | 143.00 |                  |      |
|     |                                   |                     |                     |          | Human leukemia | K562 | 460.00 |                  |      |
| 39  | P. fusca & Nigrospora oryzae PF18 | Mannitol, maltose, glucose, MSG, yeast extract, corn syrup, KH<sub>2</sub>PO<sub>4</sub>, MgSO<sub>4</sub>, artificial sea salt, and water | Mycelia | Oryzamides A | Human cervix cancer | HeLa | 16.38 | (Ding et al., 2016) |      |
|     |                                   |                     |                     |          | Oryzamides B |        | 8.52 |                  |      |
|     |                                   |                     |                     |          | Oryzamides C |        | 20.51 |                  |      |
| No. | Sponge species | Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC$_{50}$ (µg/ml) | Ref. |
|-----|----------------|------------------|---------------------|-------------------|----------|-------------|-----------|-----------------|------|
| 40  | Axinella polypoides | Clonostachys sp. | Rice and seawater | Mycelia and medium | 3-(3-Chloro-2-hydroxypropyl)-8-hydroxy-6-methoxyisochromen-1-one | Mouse lymphoma | L5178Y | n.a. | (Meng et al., 2016) |
| 41  | H. okadai | T. harzianum OUPS-111D-4 | Glucose, malt extract, peptone, and artificial seawater | Medium | Tanduykisins E | Mouse leukemia | P338 | 2.17 | (Suzue et al., 2016) |
| 42  | Cinachyrella australielsis | Aspergillus insulicola MD10-2 | Glucose, peptone, KH$_2$PO$_4$, MgSO$_4$, and artificial seawater | Mycelia | Insulicolide A | Human Lung Cancer | NCI-H460 | 2.97 | (Zhao et al., 2016b) |
| 43  | Unidentified Marine Sponge (XS-2009001) | Corynespora cassiicola OUPS-111D-4 | Rice, sea salt, and water | Mycelia and medium | Tandyukisin E | Mouse leukemia | HL-60 | 2.22 | (Suzue et al., 2016) |
| 44  | Neopetrosia chaliniformis AR-01 | Aspergillus nomius | Glucose, peptone, yeast extract, CaCO$_3$, and seawater | Mycelia and medium | Insulicolide A | Human Lung Cancer | NCI-H460 | 2.97 | (Zhao et al., 2016b) |
| 45  | P. foliacens 2016F18-1 | F. lateritium | Glucose, peptone, yeast extract, CaCO$_3$, and seawater | Medium | Pyripyropene O | Human nasopharyngeal cancer | CNE1 | 1.27 | (Cao et al., 2017) |
| 46  | Sarcomagmus muscarum | Arthrinium sp. | Rice and water | Mycelia and medium | Spiroarthinols A | Human colon cancer | Caco-2 | 1.63 | (Elissawy et al., 2017) |
| 47  | Axinella cannabina | Talaromyces rugulosus | Rice, sea salt, and water | Mycelia and medium | Talarodilactone A | Human nasopharyngeal cancer | HONE1 | 3.26 | (Küppers et al., 2017) |
| 48  | P. fusca P. heterocornis | P. lateritium | Rice, artificial sea salt, and water | Mycelia and medium | Pestalachloride B | Human colon cancer | NCI-H460 | 2.77 | (Lei et al., 2017) |
| 49  | P. fusca P. heterocornis | P. lateritium | Rice, artificial sea salt, and water | Mycelia and medium | Heterocornol A | Human nasopharyngeal cancer | SUNE1 | 6.51 | (Lei et al., 2017) |
| 50  | Niphates recondite | Stachybotrys chartarum WGC-25C-6 | Rice and water | Mycelia and medium | Chartarene C | Human colon cancer | HCT-116 | 0.20 | (Li et al., 2017) |
| 51  | Stelletta sp. | Aspergillus sydowi B05-7F-4 | Glucose, malt extract, peptone, and seawater | Mycelia and medium | Diorecinolic acid | Human nasopharyngeal cancer | KB | 3.41 | (Liu et al., 2017) |
| No. | Sponge species | Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC$_{50}$ (µg/ml) | Ref. |
|-----|----------------|-------------------|---------------------|--------------------|----------|-------------|-----------|------------------|------|
| 52  | Stylissa flabelliformis | Trichoderma reesei | Dextrose, peptone, and seawater | Medium | Extract | Burkitt’s lymphoma | Raji | 470.00 | (Setyowati et al., 2017) |
| 53  | Niphates sp. | H. sinusosae | Rice and artificial seawater | Mycelia and medium | Haplophorin A | Human colon cancer | HCT-8 | 270.00 | (Wu et al., 2017) |
| 54  | H. okadai | T. harzianum | Glucose, malt extract, peptone, and artificial seawater | Medium | Trichodermanin C | Mouse leukemia | P338 | 2.53 | (Yamada et al., 2017) |
| 55  | Epipolasis sp. | Aspergillus candidus | Rice and water | Mycelia | Preussin C | Human liver cancer | HeLa | 46.52 | (Buttachon et al., 2018) |
| 56  | Petrosia sp. | Penicillium citrinum | Malt extract, glucose, peptone, ScCl$_3$, and water | Mycelia and medium | Scalusamide A | Human skin cancer | SK-MEL-2 | n.a. | (Gu et al., 2018) |
| 57  | Haliclona fascigera | Trichrophyton sp. (WR2) | Glucose, malt extract, peptone, and seawater | Mycelia and medium | Extract | Human colon cancer | WiDr | 193.95 | (Handayani et al., 2018) |
|     | | Aspergillus sp. (WR4) | Glucose, malt extract, peptone, and seawater | Mycelia and medium | Extract | Human colon cancer | WiDr | 38.21 | |
|     | | | | | | Human breast cancer | T47D | 5861.67 | |
|     | | | | | | Human cervix cancer | HeLa | 211.55 | |
|     | | | | | | Normal cell | Vero | 357.49 | |
|     | | Trichrophyton sp. (WR 6) | Glucose, malt extract, peptone, and seawater | Mycelia and medium | Extract | Human colon cancer | WiDr | 47.36 | |
|     | | | | | | Human breast cancer | T47D | 67.08 | |
|     | | | | | | Human cervix cancer | HeLa | 118.29 | |
|     | | | | | | Normal cell | Vero | 342.94 | |
|     | | Penicillium sp. (WR 9) | Glucose, malt extract, peptone, and seawater | Mycelia and medium | Extract | Human colon cancer | WiDr | 284.28 | |
|     | | | | | | Human breast cancer | T47D | 132.74 | |
|     | | | | | | Human cervix cancer | HeLa | 118.29 | |
|     | | | | | | Normal cell | Vero | 342.94 | |
| 58  | Callyspongia sp. | Nocardiosis sp. UR67 | Dextrose, malt extract, peptone, yeast extract, and artificial seawater | Medium | Nocardiodite A | Human myeloma | MM.1S | 6.15 | (Ibrahim et al., 2018) |
| 59  | Agelas oxydes | Aspergillus carneus | Rice, sea salt, and water | Mycelia and medium | Isopropylchalcone | Mouse lymphoma | L5178Y | 0.18 | (Özkaya et al., 2018) |
| 60  | Callyspongia sp. | Alternaria alternata strain SCAU091 | Rice, sea salt, and water | Mycelia and medium | Altenorxin VII | Human leukemia | K562 | 0.10 | (Pang et al., 2018) |
| 61  | Stylissa flabelliformis | T. reesei strain TV221 | Dextrose, peptone, and seawater | Medium | Extract | Human colon cancer | WiDr | 88.88 | (Setyowati et al., 2018) |
| No. | Sponge species | Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type          | Cell line | IC$_{50}$ (µg/ml) | Ref.            |
|-----|----------------|------------------|---------------------|--------------------|----------|----------------------|-----------|-------------------|----------------|
| 62  | *Stylissa* sp. | *Aspergillus* flocculosus | Rice, yeast extract, KH$_2$PO$_4$ and seawater | Mycelia and medium | Ochraceopone F | Human colon cancer   | HCT-15    | n.a.              | (Shin et al., 2018) |
|     |                |                  |                     |                    |          | Human gastric cancer | NUGC-3    | n.a.              |                 |
|     |                |                  |                     |                    |          | Human lung cancer    | NCI-H23   | n.a.              |                 |
|     |                |                  |                     |                    |          | Human kidney cancer  | ACHN      | n.a.              |                 |
|     |                |                  |                     |                    |          | Human prostate cancer| PC-3      | n.a.              |                 |
|     |                |                  |                     |                    |          | Human breast cancer  | MDA-MB-231| n.a.             |                 |
| 63  | *Callyspongia* sp. | *Didymellaceae* sp. SCSIO F46 | Rice, sea salt, and water | Mycelia | Diorcinols L | Human leukemia | K562 | 12.53             | (Tian, et al., 2018a) |
|     |                |                  |                     |                    |          | Human breast cancer  | K562      | 3.03              |                 |
|     |                |                  |                     |                    |          | Human lung cancer    | A-549     | 5.10              |                 |
|     |                |                  |                     |                    |          | Human lung cancer    | Huh-7     | 1.64              |                 |
|     |                |                  |                     |                    |          | Human lung cancer    | H1975     | 4.41              |                 |
|     |                |                  |                     |                    |          | Human cervix cancer  | HeLa      | 2.05              |                 |
|     |                |                  |                     |                    |          | Normal cell          | HL7702    | 19.65             |                 |
|     |                |                  |                     |                    |          | Human leukemia       | HL60      | 2.77              |                 |
|     |                |                  |                     |                    |          | Human leukemia       | MOLT-4    | n.a.              |                 |
|     |                |                  |                     |                    |          | Human prostate cancer| DU145     | 2.62              |                 |
| 64  | *Callyspongia* sp. | *Aspergillus* sp. SCSIO XWS02F40 | Rice, sea salt, and water | Mycelia | Protuboxepin C | Human lung cancer   | A-549     | 40.72             | (Tian, et al., 2018b) |
|     |                |                  |                     |                    |          | Human cervix cancer  | HeLa      | 24.84             |                 |
| 65  | *P. fusca* | *Gliomastix* sp. ZSDD1-F7-2 | Rice, sea salt, and water | Mycelia | Gliomasolide F | Human cervix cancer | HeLa      | n.a.              | (Zhang et al., 2018) |
| 66  | Unidentified marine sponge | *Aspergillus* sp. SCSIO XWS03F03 | Rice, sea salt, and water | Mycelia | Missztrine A | Human liver cancer  | HepG-2    | n.a.              | (Zhou et al., 2018) |
|     |                |                  |                     |                    |          | Human leukemia       | HL60      | 1.14              |                 |
|     |                |                  |                     |                    |          | Human cervix cancer  | HeLa      | n.a.              |                 |
|     |                |                  |                     |                    |          | Human skin cancer    | A375      | n.a.              |                 |
|     |                |                  |                     |                    |          | Human lung cancer    | A-549     | > 10.98           |                 |
|     |                |                  |                     |                    |          | Human colon cancer   | HT-29     | > 10.98           |                 |
|     |                |                  |                     |                    |          | Human breast cancer  | SK-BR-3   | > 10.98           |                 |
|     |                |                  |                     |                    |          | Human prostate cancer| LN-caP    | 1.81              |                 |
|     |                |                  |                     |                    |          | Human breast cancer  | MCF-7     | > 10.98           | (Artasasta et al., 2019) |
| 67  | *Neopetrsia* chaliniformis | *A. nomius* NC06 | Rice and water | Mycelia | Fraction I | Human colon cancer   | HCT-116   | 193.64            | (Artasasta et al., 2019) |
|     |                |                  |                     |                    |          | Fraction II          |          | 5.28              |                 |
|     |                |                  |                     |                    |          | Fraction III         |          | 15.82             |                 |
|     |                |                  |                     |                    |          | Fraction IV          |          | 10.27             |                 |
|     |                |                  |                     |                    |          | Fraction V           |          | 45.27             |                 |
| 68  | *Agelas* oroides | *P. canescens* | Rice, artificial sea salt, and water | Mycelia | Bromophilone A | Mouse lymphoma      | L5178Y    | 9.98              | (Frank et al., 2019) |
|     |                |                  |                     |                    |          | Human ovarian cancer  | A2780     | 1.94              |                 |
| 69  | Unidentified marine sponge | *Aspergillus* sp. SCSIO41018 | Rice, artificial sea salt, and water | Mycelia | Asterriquinones I | Human leukemia      | K562      | 9.85              | (Guo et al., 2019) |
|     |                |                  |                     |                    |          | Human liver cancer   | BEL-7042  | 14.20             |                 |
|     |                |                  |                     |                    |          | Human gastric cancer | SGC-7901  | 16.07             |                 |
|     |                |                  |                     |                    |          | Human lung cancer    | A-549     | > 10.51           |                 |
|     |                |                  |                     |                    |          | Human cervix cancer  | HeLa      | > 10.51           |                 |
| 70  | *Axinella* polypoides | *Talaromyces brunneus* | Rice, artificial sea salt, and water | Mycelia | Extract | Human colon cancer   | HCT-116   | 165.12            | (Heydari et al., 2019) |
| 71  | *Haliclona* sp. | *Aspergillus* sp. LS45 | Rice, sea salt, and water | Mycelia | Aspergilactones A | Human leukemia      | CCRF-CEM  | n.a.              | (Huang, et al., 2019b) |
|     |                |                  |                     |                    |          | Human leukemia       | K562      | n.a.              |                 |
| No. | Sponge species | Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC<sub>50</sub> (µg/ml) | Ref. |
|-----|----------------|------------------|---------------------|--------------------|----------|-------------|-----------|----------------------|-----|
| 72  | Hymeniacidon sp. | Aspergillus sp. NBUF87 | Rice, sea salt, and water | Mycelia | Aspergilmarins A | Human leukemia | CCRF-CEM | > 13.30 | (Huang, et al., 2019a) |
| 73  | P. fusca | Pestalotiopsis sp. XWS03F09 | Rice, artificial sea salt, and water | Mycelia | Heterocornols O | Human gastric cancer | BGC-823 | 9.17 | (Lei, et al., 2019) |
| 74  | Haliclona sp. | Aspergillus sp. LS34 | Potato, dextrose, sea salt, water | Medium | Asperther A | Human leukemia | CCRF-CEM | 7.46 | (Li, et al., 2019) |
| 75  | P. fusca | A. sydowii SCSIO4130 | Mannitol, maltose, glucose, MSG, KH<sub>2</sub>PO<sub>4</sub>, MgSO<sub>4</sub>, yeast extract, and water | Medium | Aspergilloses D | Human leukemia | K562 | n.a. | (Liu, et al., 2019) |
| 76  | Callyspongia sp. | Aspergillus terreus SCSIO 41008 | Potato, mannitol, maltose, glucose, peptone, yeast extract, MSG, sea salt, and water | Mycelia and medium | Aspergillamides C | Human glioblastoma | U87 | n.a. | (Luo, et al., 2019b) |
| 77  | Callyspongia sp. | A. versicolor SCSIO 41016 | Rice, artificial sea salt, and water | Mycelia and medium | Protuboxepin G | Human kidney cancer | ACHN | 10.13 | (Luo, et al., 2019a) |
| 78  | Callyspongia sp. | A. versicolor SCSIO 41013 | Rice, sea salt, and water | Mycelia | Versispiroketal A | Human globlastoma | SF-268 | 26.08 | (Salendra, et al., 2019b) |
| 79  | Callyspongia sp. | P. citrinum SCSIO 41017 | Rice, sea salt, and water | Mycelia | Xerucitrinic acid A | Human globlastoma | SF-268 | 4.95 | (Salendra, et al., 2019a) |
| 80  | H. okadai | T. harzianum | Glucose, malt extract, peptone, and artificial seawater | Mycelia and medium | Trichodermanins F | Mouse leukemia | P338 | 15.67 | (Yamada, et al., 2019) |
| 81  | Haliclona fascigera | Cochliobolus goniculatus WR12 | Rice and water | Mycelia | Radicinin | Human colon cancer | WiDr | 47.17 | (Handayani, et al., 2020b) |
| 82  | Chelonaphysilla sp. | Aspergillus flavus | Rice and water | Mycelia | Extract | Human breast cancer | T47D | 743.42 | (Handayani, et al., 2020a) |
Table 1. Classification of cytotoxic activity of compound from marine sponge-derived fungi.

| No. | Sponge species | Fungi association | Fermentation medium | Extraction specimen | Compound | Cancer type | Cell line | IC$_{50}$ (µg/ml) | Ref. |
|-----|----------------|-------------------|---------------------|--------------------|----------|-------------|-----------|-------------------|------|
| 83  | Dactylospongia sp. | Cladosporium halotolerans MN859971 | Malt extract, artificial sea salt, and water | Mycelia and medium Extract (Dc03) | Human breast cancer | T47D | 225.75 | (Sandrawati et al., 2020) |
|     |                | P. citrinum MN859968 | Malt extract, artificial sea salt, and water | Mycelia and medium Extract (Dc04) |             |             |          | 640.12           |      |
|     |                | A. versicolor MN859970 | Malt extract, artificial sea salt, and water | Mycelia and medium Extract (Dc05) |             |             |          | 1760.98          |      |
|     |                | A. sydowii MN859970 | Malt extract, artificial sea salt, and water | Mycelia and medium Extract (Dc08) |             |             |          | 456.75           |      |
| 84  | Unidentified marine sponge Trichoderma licii 15G49-1 | Rice and artificial seawater | Mycelia DC1149B | Human pancreatic cancer | PANC-1 | 366.36 | (Tang et al., 2020) |
| 85  | Unidentified marine sponge (No. XS-3) A. candidus OUCMDZ-1051 | Mannitol, glucose, maltose, yeast extract, glutamate, corn syrup, CaCO$_3$, KH$_2$PO$_4$, MgSO$_4$, and seawater Medium | 4-O-Methylcandidusin A | Human leukemia | MV4-11 | 0.61 | (Wang et al., 2020a) |
|     |                    |                   |                      |                    | Human leukemia | K562 | 8.46 |
|     |                    |                   |                      |                    | Human lung cancer | A-549 | 1.98 |
|     |                    |                   |                      |                    | Human leukemia | HL-60 | 1.52 |
|     |                    |                   |                      |                    | Human glioblastoma | U87 | 36.60 |
|     |                    |                   |                      |                    | Human glioblastoma | U251 | 6.99 |
|     |                    |                   |                      |                    | Human breast cancer | MCF-7 | 2.84 |
|     |                    |                   |                      |                    | Human prostate cancer | DU145 | 0.66 |
|     |                    |                   |                      |                    | Human breast cancer | MDA-MB-231 | 0.69 | (Wang et al., 2020b) |
|     |                    |                   |                      |                    | Human leukemia | HL-60 | 2.59 |
|     |                    |                   |                      |                    | Human cervix cancer | HO8910 | 6.99 |

**Figure 1.** Distribution of conducted studies about cytotoxic activity of marine sponge-derived fungi. *June 2020.*

**Figure 2.** Classification of the component activity according to their IC$_{50}$ values.

**Classification of cytotoxic activity of compound from marine sponge-derived fungi**

In this review, we provide an overview of the bioactive metabolites extracted and isolated from marine sponge-derived fungi exhibiting *in vitro* cytotoxic activity in cell line cancer. By comparing the IC$_{50}$ values, the units in nM, M, and ng/ml are converted into µg/ml unit by adjusting the molecular weight of the compound. All components were classified based on the IC$_{50}$ value following the definition of Weerapreeyakul et al. (2012), which classifies the activity of cytotoxic components into “very strong cytotoxic”: IC$_{50}$ is < 10 µg/ml; “strong cytotoxic”: IC$_{50}$ is 10–100 µg/ml; and “moderate cytotoxic”: IC$_{50}$ is 100–500 µg/ml. What needs to be noted is that the test was administered with different cell line cancers, so there is a possibility that the inactive component in one cell line cancer could have a different IC$_{50}$ value in another type of cell line cancer. It would be wise to reevaluate the activity of the inactive components obtained from marine sponge-derived fungi using other cancer cell lines (Badisa et al., 2009; Sutejo et al., 2016; Weerapreeyakul et al., 2012).

The bioactive components studied were 132 components extracted and isolated from marine sponge-derived fungi. These 132 components consist of 16 extracts, 5 fractions, and 111 isolates. As shown in Figure 2, among the observed bioactive components, there are 56 components with very strong cytotoxic
activity, 31 components with strong cytotoxic activity, and 15 components with moderate cytotoxic activity against various cell line cancers. There are 16 components that cannot be classified because they have IC$_{50}$ values > 500 µg/ml and have less accurate and clear IC$_{50}$ values reported in the article. Furthermore, they cannot be included in that classification. There are 14 components reported to have no cytotoxic activity. The component is inactive only in some cell line cancers, and testing on other types of cell line cancers has not been conducted to see its cytotoxic activity (Badisa et al., 2009; Sutejo et al., 2016; Weerapreyyakul et al., 2012).

In this review, 27 types of cancer were found used in the study to determine the cytotoxic activity of marine sponge-derived fungi. The most common types of cancer are human leukemia, human colon cancer, human lung cancer, human cervix cancer, and human breast cancer. It is in line with the report by Bray et al. (2018) in which this type of cancer is reported to have a high incidence rate worldwide in humans, and even this type of cancer is included in the top 10 cancers causing death in humans. It has triggered many researchers to focus on these five types of cancer by exploring new compounds coming from the sea, especially marine sponge-derived fungi (Thomas et al., 2010). Potential compounds from marine sponge-derived fungi are expected to be used as new drugs in cancer treatment. To conduct a brief test of anticancer activity, researchers used in vitro cell line cancer to facilitate the screening of the anticancer activity of components obtained from marine sponge-derived fungi. In this review, we identified 317 types of cell line cancers used in determining the cytotoxic activity of components obtained from marine sponge-derived fungi. The most common types of cell line cancer are human cervix cancer (HeLa), human lung cancer (A-549), human leukemia (HL-60), mouse leukemia (P338), human liver cancer (HepG-2), human colon cancer (HCT-116), and human breast cancer (MCF-7). The use of this type of cell line cancer is based on the cancer incidence rates mentioned previously. Furthermore, there are factors which considered the use of this cell line cancer. These factors include easiness to handle and manipulate, high homogeneity, high degree of similarity with the initial tumor, large number and variety of cancer cell lines available, immediate accessibility to the scientific community, unlimited autoreplicative source, continuous cell lines, easy substitution of contaminated cultures for the respective frozen cell lines, and reproducibility of results in the correct conditions (Ferreira et al., 2013). Moreover, cell lines which are normal cells are also used. The use of normal cell lines aims to determine the cytotoxic strength of a sample that only damages cancer cells and does not damage normal cells of living things. The comparison of the IC$_{50}$ value between normal cell line and cancer cell line produces a value called selectivity index (SI). Compounds or extracts having a SI > 3 have high selectivity in certain cancer cells (Badisa et al., 2009; Sutejo et al., 2016). The normal cell lines that are often used in cytotoxic-related research in this review are Vero (monkey epithelial kidney) and HL7702 (human normal liver).

The components isolated from marine sponge-derived fungi classified as very strong cytotoxic are shown in Table 2. Xanthone derivatives are metabolites generally distributed in higher plants and several types of fungi. This metabolite has several biological activities, such as antimicrobial, antiviral,

| No. | Compound                                      | Cell line cancers                              |
|-----|-----------------------------------------------|------------------------------------------------|
| 1   | 4,6-Dimethoxy-2,9-dimethyl dibenz[c,e][1,4]-  | HL-60                                          |
|     | dioxine-1,7-diol                              |                                                |
| 2   | 4-O-Methylcandidusia A                        | A-549; DU145; H1975; HL-60; K562; MCF-7; MDA-  |                                                |
|     |                                               | MB-231; MV-4-11; U251                          |                                                |
| 3   | Anomalin A                                    | A2780; A2780CsR; L5178Y                       |                                                |
| 4   | Aspergilides A                                | L1210                                          |                                                |
| 5   | Aspergilides C                                | L1211                                          |                                                |
| 6   | Asperther A                                   | CCRF-CEM                                      |                                                |
| 7   | Bromophiline A                                | A2780; L5178Y                                 |                                                |
| 8   | Chartarene C                                  | A2780; HCT-116; HepG-2; NCI-H1655             |                                                |
| 9   | Corynesidone A                               | HeLa                                           |                                                |
| 10  | Corynethers A                                | HL-60                                          |                                                |
| 11  | Cyclic tetrapeptide WF-316                    | L5178Y                                        |                                                |
| 12  | Cytochalasin K                               | A-549; H1975; HL-60; HeLa; L5178; Huh-7;      |                                                |
|     |                                               | K562; MOLT-4                                   |                                                |
| 13  | D ankastatin C                                | P338                                           |                                                |
| 14  | D ankasterone                                 | P338                                           |                                                |
| 15  | D ankasterones A                              | P338                                           |                                                |
| 16  | D ankasterones B                              | P338                                           |                                                |
| 17  | Diorecinols L                                 | A-549; DU145; H1975; HeLa; HL-60; Huh-7;      |                                                |
|     |                                               | MCF-7                                          |                                                |
| 18  | Disydolon C                                   | HeGp-2                                         |                                                |
| 19  | Efrapeptin G                                  | HCT-116; HeLa; HT-29; SK-BR3                   |                                                |
| 20  | Epoxyphomalin A                              | BXF 1218 L; BXF T24; CNXF 498NL; DU145;       |                                                |
|     |                                               | GXF 251 L; HCT-116; HT-29; LN-cap; LXF 1121   |                                                |
|     |                                               | L; LXF 289 L; LXF 526 L; LXF 529 L; LXF 629   |                                                |
|     |                                               | L; MAXF 401NL; MCF-7; MEXF 276; MEXF 394NL;   |                                                |
|     |                                               | MEXF 462NL; MEXF 514 L; MEXF 520 L; NCI-H460; |                                                |
|     |                                               | OVXF 1619 L; OVXF 899 L; OVXF OVCA-3; PANC1; |                                                |
|     |                                               | PAXF 1657 L; PRXF 22RVL; PRXF PC3M; PXF 1752  |                                                |
|     |                                               | L; RXF 1781 L; RXF 393NL; RXF 468 L; RXF       |                                                |
|     |                                               | 944 L; SF-268; UXF 1138 L                     |                                                |
| 21  | Ester of (E,E)-6-oxo-2,4-hexadienoic acid    | HeLa; L5178Y; PC-12                           |                                                |
| 22  | Fellutamide C                                | HCT-15; SK-MEL-2; XF-498                      |                                                |
| 23  | Fellutamide F                                 | A-549; HCT-15; SK-MEL-2; SK-OV-3; XF-498     |                                                |
| 24  | Fraction II                                   | HCT-116                                       |                                                |
| 25  | Grisephenone A                               | HeLa; U937                                    |                                                |
| 26  | Gymnastatin A                                | P338                                           |                                                |
| 27  | Gymnastatin F                                | P338                                           |                                                |
| 28  | Gymnastatin G                                | P338                                           |                                                |
| 29  | Gymnasterones B                              | P338                                           |                                                |
| 30  | Gymnasterones C                              | P338                                           |                                                |
| 31  | Gymnasterones D                              | P338                                           |                                                |
| 32  | Hetercoronol A                               | BCG-823; NCI-H460; SMMMC-7721                 |                                                |
| 33  | Hetercoronols O                              | 786-0; BGC-823                                |                                                |
| 34  | IB-01212                                     | HeLa; HT-29; LN-cap; SK-BR3                    |                                                |
| 35  | Insulicolide A                               | NCI-H460                                      |                                                |
| 36  | Isopropylchaetomi-nine                       | L5178Y                                        |                                                |
| 37  | Marilones C                                  | MCF-7; SF-268                                 |                                                |
| 38  | Methyl averatin                              | A-549; HCT-15; SK-MEL-2; SK-OV-3; XF-498     |                                                |
| 39  | Nocartoidite A                               | CT26; HeLa; MM.15                             |                                                |

Table 2. List of compounds with very strong cytotoxic activity based on the IC$_{50}$ value.
antitubercular, and anticancer. Anomalin A (1) is one of the xanthones derived from the fungus Arthrinium sp. which is associated with the sponge Geodia cydonium (see Fig. 3) (Abdel-Latif et al., 2003; Ebada et al., 2011; Morel et al., 2000; Peres et al., 2000).

Bioactive polyketide derivatives include bromophilone A (2), exophyphomalin A (6), heterocornol A (9), heterocornol O (10), and oxalicumone A (14) (Fig. 3). Bromophilone A (2) is a polyketide azaphilone group with a bicyclic core and conjugated chromophore which has a bromide atom as a substituent. This metabolite is the combined result of the fungal fermentation media of Penicillium canescens with NaBr. Exophyphomalin A (6) derived from the fungus Phoma sp. associated with the sponge Ectypalia perox is a very active component in many cancer cell lines and this component has the potential to be developed for future cancer therapy. Heterocornol A (9) and heterocornol O (10) are polyketide derivatives derived from the fungi of the genera Pestalotiopsis associated with the sponge Phakellia fusca. Both these components have an IC_{50} ranging from 2 to 10 µg/ml in some cancer cells. Oxalicumone A (14) is a chromone-type bioactive polyketide derivative to be precise, dihydrothiophene-condensed chromone. This bioactive component comes from Aspergillus sp. LS34 associated with the sponge Haliclona sp. possessing very strong cytotoxic activity in the cancer cell lines CCRF-CEM and K562 (Frank et al., 2019; Gao et al., 2013; Lei et al., 2017a, 2019; Li et al., 2019; Mohamed et al., 2009; Sun et al., 2013; Wang et al., 2018).

Cytochalasins are a group of metabolites that are often found in fungi in several genera, such as Phomopsis, Chalara, Hypoxylon, Xylaria, Daldinia, Pseudocurtum, and Phoma exigua. Cytochalasin K (3) is a metabolite of the marine sponge-derived fungi Arthrinium arundinis ZSDS1-F3 (Fig. 3). This class of metabolites is unique in its structure with a macrocyclic ring with antitumor, antibacterial, and HIV-1 protease inhibition activity. The most unusual activity of this metabolite is the ability to make the cell secrete its nucleus resulting in the formation of a cell without a nucleus (Liu et al., 2006; Wang et al., 2015). Diocinols L (4) is a phenol derivative metabolite (Fig. 3). This metabolite comes from the fungus Didymellaceae sp. SC510 F46 in association with Calyspongia sp. sponge. These phenol derivatives have strong cytotoxic activity in a number of cancer cell lines, including A-549, DU145, H1975, HeLa, HL60, Huh-7, and MCF-7 (Tian et al., 2018a). Acremonium sp. associated with the Teichaxinella sp. sponge produces several types of bioactive metabolite groups from the polyketides, hydroquinones, ketide-terpenes, alkaloids, and terpene glycosides. Efrapeptin G (5) is a new bioactive metabolite from the peptidebiotic class derived from the fungus (Fig. 3). This bioactive metabolite has a very strong cytotoxic activity in several cancer cell lines, such as HCT-116, HeLa, HT-29, and SK-BR3 (Boo et al., 2006).

Fellutamide C (7) and fellutamide F (8), components belonging to the lipopeptide group, have an IC_{50} of 0.1–3 µg/ml (Fig. 3). Both are derived from the fermentation of the fungus Aspergillus versicolor which is associated with the sponge Petrosoi sp. growing on the coast of Jeju Island, Korea (Lee et al., 2010a; Lee et al., 2011). The new bioactive component IB-01212 (11) occurring from the fungus Clonostachys sp. ESNA-A009 has a very strong cytotoxic activity with an IC50 0.01 µg/ml (Fig. 3). This compound belongs to the cyclodepsipeptide group. Currently, IB-01212 (11) is being developed for biosynthetic so that it can be mass-produced without isolating it from fungi (Cruz et al., 2006).
The bioactive phthalides group has activities such as a modulation of the central nervous system, protection against brain ischemia, modulation of platelet aggregation and heart function, inhibition of smooth muscle cell proliferation, antiaggregant activity, and smooth muscle relaxation, as well as antibacterial, antifungal, antiviral, and phytotoxic activity. Phthalides are secondary metabolites produced naturally by several types of fungi that are associated with the marine ecosystems, such as Ascochyta, Aspergillus, Alternaria, Penicillium, Hericium, or Talaromyces. Stachylium sp. are associated with the sponge Callyspongia sp. cf. C. flammaea producing marilone C (12) components included in the phthalides group (Fig. 3) (Almeida et al., 2011).

Aspergillus versicolor associated with the sponge Petro西亚 sp. produces the bioactive component methyl averantin (13) (Fig. 3). This secondary metabolite is included in the anthraquinone group. Methyl averantin (13) has very strong cytotoxic activity with an IC₅₀ range 0.4–1.1 µg/ml in cancer cell lines like A-549, HCT-15, SK-MEL-2, SK-OV-3, and XF-498 (Lee et al., 2010b). As one of the most widespread genera of endophytic fungi, Pestalotiopsis produces various bioactive secondary metabolites. Pestalachloride B (15) is a metabolite of the fungal species Pestalotiopsis heterocornis associated with P. fusca which has cytotoxic activity with IC₅₀ ranging from 2 to 10 µg/ml in cancer cell lines BCG-823, NCI-H460, and SMMC-7721 (Fig. 3) (Li et al., 2017b; Li et al., 2008). Pyripyropene O (16) and trichodermann C (18) are components belonging to the terpenes group (Fig. 3). Pyripyropene O (16) is pyripyrpenes derived from sesquiterpenes conjugated with a-pyrene and pyridine moieties. Pyripyrpenes are representative metabolites of several genera of fungi, such as Aspergillus and Penicillium. The bioactive metabolite pyripyrpeno O (16) is derived from Fusarium lateritium (2016F18-1 which is associated with the sponge Phyllospongia foliascens. Trichodermann C (18) is classified as terpene with a rare fused 6-5-6-6 ring system. This bioactive metabolite comes from the fungus Trichoderma harzianum OUPS-111D-4 associated with the Halichondria okadai sponge (Cao et al., 2017; Yamada et al., 2017).

The secondary metabolites with an alkylated decaolin skeleton have various bioactivities, such as antibacterial, antifungal, and phytotoxicity. There are many decaolin derivatives including tandyukisin E (17) and trichoharzin (19) (Fig. 3). These two components are bioactive metabolites of the fungus T. harzianum OUPS-111D-4 associated with the H. okadai sponge. Tandyukisin E (17) has a unique chemical structure with a different side chain from the tandyukisin obtained so far and has cytotoxic activity in cancer cell lines HL-60, L1210, and P338 with IC₅₀ values of 2.22, 3.59, and 2.17 µg/ml, respectively. Trichoharzin (19) is a polyketide constructed with an alkylated decaolin skeleton and esterified with 3-methylglutaconic acid, a rare acyl moiety. This bioactive metabolite has cytotoxic activity in cell line HL-60 with IC₅₀ = 6.66 µg/ml (Kobayashi et al., 1993; Suzue et al., 2016; Yamada et al., 2014). Emericella variecolor associated with the sponge Cinachyrella sp. produces several metabolites of the lactones group. Varioxiranol K (20) is one of the bioactive metabolites of this fungus (Fig. 3). These bioactive metabolites have very strong cytotoxic activity in cancer cell lines like A2780, BGC-823, CHT-116, HepG-2, and NCI-H1650 with an IC₅₀ range of 1–4 µg/ml (Wu et al., 2015).

Influences of the fermentation conditions from marine sponge-derived fungi to produce cytotoxic metabolite

Metabolites produced by microbes are divided into two, primary metabolites and secondary metabolites. The production of primary metabolites is considered important, for instance, ethanol, citric acid, polysaccharides, acetone, butanol, and vitamins. Secondary metabolites produced by microbes include antibiotics, growth promoters, enzyme inhibitors, and others (Stanbury et al., 1995). Marine sponge-derived fungi produce a large number of new bioactive secondary metabolites, some of which exhibit new molecular structures that have never been previously found in nature. To be able to produce bioactive metabolites, the fungi associated with the sponge must first be isolated from the host and then fermented with a liquid medium of which composition is as close as possible to the state when it is in the host (Kjer et al., 2010).

In this review, we identified 11 types of carbon sources used in the fermentation media for marine sponge-derived fungi, including rice (38 media), glucose (33 media), malt extract (30 media), dextrose (9 media), and potato (8 media). Fungi require a greater amount of carbon than other essential elements because half of the dry weight of the fungal cell is estimated to consist of carbon which is important in the formation of the fungal cell wall (Moore-Landecker, 1996). The source of complex carbon in the medium is converted by the fungus into a simpler form that can be metabolized. Currently, rice and malt extract is widely used by researchers as a source of carbon in the medium. These two complex carbon sources, after being sterilized by heating, split into simpler carbon which could be used by fungi in their metabolism, with the result that these two carbon sources are widely used in the protocol for fermentation of marine sponge-derived fungi to produce new bioactive compounds, especially those useful for cancer (Kjer et al., 2010; Muthukumar et al., 2013).

Some of the fungal isolates associated with the marine environment include Culpicalta achraspera Meyers and Moore, Humicola alopallonella Meyers and Moore, Orbozyme spectabilis Linder, Halosphaeria mediotigerec Cribb and Cribb, Penicillium decumbens, Penicillium chrysogenum, Acremonium strictum, Fusarium fujikuroi, and Fusarium sporotrichioides, which have a dry weight of mycelia developing with increasing levels of carbon sources in the fermentation media (Fuentes et al., 2015; Sguros and Simms, 1963). Trichoderma lignorum has increased conidia and hyphae growth when the carbon source is increased, but its growth decreases when the concentration of the carbon source exceeds 10 times of the frequent use (Seto and Tazaki, 1975). The effect of various carbon sources on the growth of Trichoderma viride species shows that the maximum production of secondary metabolites resulting from the highest to lowest production is influenced by the carbon sources of sucrose, glucose, cellulose, maltose, and carboxymethyl cellulose with an optimum level of 1%–15% (Gautam et al., 2010).

There are five types of nitrogen sources that we can identify in this review including peptone (30 media), yeast extract (16 media), glutamate (6 media), NaNO₃ (2 media), and tryptophan (2 media). The nitrogen source in the marine sponge-derived fungi fermentation media does not appear to be present in the medium given its use which is not as much as the carbon source. Nitrogen sources are one of the important elements in the growth of endophytic fungi; however, nitrogen sources are not very influential in the growth of fungi and in the formation of secondary metabolites, except for metabolites containing nitrogen.
in their molecules. The use of peptone as a nitrogen source in the medium gives a high increase in mycelia dry weight compared to the use of inorganic nitrogen sources such as NaNO3 and NH4Cl (Hussain et al., 2003; Khattabi et al., 2004; Muthukumar et al., 2013).

Halophilic microorganisms can grow at high levels of salinity, for instance, in the sea with 3% NaCl. The salinity of a microorganism growth environment causes differences in osmotic pressure. Increasing levels of salinity exceeding the salinity of seawater resulted in several species of associated fungi from the sea decreasing their growth rates, but the unavailability of salinity inhibits the growth of these associated fungi from the sea. Several genera of associated fungi including Penicillium (32 strains), Aspergillus (10 strains), Mycelia sterilia (3 strains), Fusarium (1 strain), and Paeucilomyces (1 strain) were isolated from several samples, such as seaweed, underwater sediments, and mangrove roots which have optimal growth and have the widest colony diameter found in fungi grown on medium with 3%–6% NaCl. The antimicrobial activity of these associated fungi in C. albicans showed the highest activity when treated with 6%–9% NaCl (Huang et al., 2011). The use of seawater or sea salt in the marine sponge-derived fungus fermentation media is very important because when living in its host, the surrounding environment of the fungus is a sea with salinity levels adjusting to the surrounding sea conditions. In this review, we identified 70 fermentation media using conditions such as in the sea, using natural seawater and sea salt, artificial seawater, and sea salt, while 26 media do not use conditions such as the origin of the fungus. The identification results show that the medium using seawater components (natural or artificial) produces bioactive components with very strong cytotoxic activity. The addition of components such as KH2PO4, MgSO4, MnCl2, and KCl in a medium which do not use seawater components also makes the fungi produce active metabolites as cytotoxic. Several genera of Trichoderma associated with the marine environment have optimal growth and dry weight mycelial at salinity levels of 1%–2%, but salinity levels that exceed 3% reduce the growth of fungal colonies (Bheemaraya et al., 2013; Mishra et al., 2016; Sánchez-Montesinos et al., 2019).

In this review, we classify the extracted specimens to obtain bioactive components from marine sponge-derived fungi into medium part, part mycelia, and both. The extraction process using both parts of mycelia and medium is the decision that most researchers do to extract bioactive components from fermentation. It is possible because the bioactive components are not yet known whether they are in the fungal cell or excreted out of the cell; therefore, the use of the extraction process for these two parts results in an optimal extraction. Furthermore, the extraction results using these two parts on average produce bioactive components containing a very strong cytotoxic activity (Kjer et al., 2010).

CONCLUSION

The data presented in the review show the potential of marine sponge-derived fungi as producing metabolites with cytotoxic activity and can reduce exploitation of rare sponges to produce bioactive components in cancer therapy. The components have been summarized and the most promising components are polyketide derivatives, lipopeptides, cyclo depsipeptides, decalin derivatives, xanthone derivatives, phenol derivatives, cytochalasins, peptaibiotics, phthalides, anthraquinone, terpenes, decalin derivatives, and lactones. In producing bioactive metabolites for cytotoxicity, the fermentation media is essential. Carbon sources, nitrogen, salinity, and extracted specimens are factors in the production of bioactive metabolites for cytotoxic fungi from marine sponges. A comprehensive approach is needed to evaluate the specific mechanism of action of the bioactive component as an anticancer. For further large-scale development in evaluating the production of bioactive metabolites from marine sponge-derived fungi, it may be necessary to develop components of the fermentation media which are more specific to certain fungi.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

ETHICAL APPROVAL

This study does not involve the use of animals or human subjects.

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