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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 IC_{50}, 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 antimalarial, 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*.,

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2017). 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 IC_{50} 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 *Callyspongia*, *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, antitumor, 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*	*Gymnasella dankaliensis*	Malt, glucose, peptone, and artificial seawater	Mycelia	Gymnastatins A	Mouse leukemia	P338	18.00	(Numata *et al*., 1997)
					Gymnastatins B			108.00	
					Gymnastatins C			106.00	
2	*H. okadai*	*T. harzianum* OUPS-N 115	Glucose, peptone, malt, and artificial seawater	Medium	Trichodenone A	Mouse leukemia	P338	0.21	(Amagata, *et al*., 1998b)
					Trichodenone B			1.21	
					Trichodenone C			1.45	
					Harzialactone B			60.00	
3	*Halichondria japonica*	*G. dankaliensis*	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. dankaliensis*	Malt, glucose, peptone, and artificial seawater	Mycelia	Dankasterone	Mouse leukemia	P338	2.20	(Amagata *et al*., 1999)
5	*Zyzyya* sp.	*Penicillium brocae*	Sucrose, salt ($NaNO_3$, KH_2PO_4, $MgSO_4$, KCl, $FeSO_4$), 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	Jurkat	> 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. dankaliensis*	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 ($NaNO_3$, K_2PO_4, $MgSO_4$, KCl, $FeSO_4$), and seawater	Medium	Efrapeptin G	Human colon cancer	HCT-116	0.01	(Boot *et al*., 2006)
9	Unidentified marine sponge	*Clonostachys* sp. ESNA-A009	Glucose, beef extract, yeast extract, starch, tryptone, NaCl, KCl, $MgCl_2$, and water	Mycelia	IB-01212	Human prostate cancer	LN-caP	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 solubles, 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. dankaliensis*	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 (from media B)			10.10	
					Gymnasterones B (from media B)			1.60	
					Gymnasterones C (from media B)			0.90	
					Gymnasterones D (from media B)			2.50	
12	*Mycale plumose*	*Penicillium aurantiogriseum*	Sorbitol, maltose, glutamine, KH_2PO_4, $MgSO_2$, tryptophan, yeast extract, and seawater	Medium	Aurantiomide B	Mouse leukemia	P338	54.00	(Xin *et al*., 2007)
						Human leukemia	HL-60	52.00	
					Aurantiomide C	Mouse leukemia	P338	48.00	
						Human liver cancer	BEL-7402	62.00	
13	Unidentified marine sponge	*Aspergillus ostianus* strain 01F313	Potato, dextrose, bromine, and water	Medium	Aspergillides A	Mouse leukemia	L1210	2.10	(Kito *et al*., 2008)
					Aspergillides B			71.00	
					Aspergillides C			2.00	

No.	Sponge species	Fungi association	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)
		Petriella sp.	Barley, spelt whole grain flakes, soy peptone, $MnCl_2$, and water	Mycelia and medium	Cyclic tetrapeptide WF-3161	Mouse lymphoma	L5178Y	< 0.10	
15	*Tethya aurantium*	*Scopulariopsis brevicaulis* 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)
						Human pancreatic cancer	Panc89	> 10.00	
						Human colon cancer	HT-29	> 10.00	
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	Epoxyphomalin A	Human bladder cancer	BXF 1218 L	0.02	(Mohamed *et al*., 2009)
							BXF T24	0.04	
						Human glioblastoma	CNXF 498NL	0.02	
							SF-268	0.35	
						Human colon cancer	HCT-116	0.33	
								0.20	
						Human gastric cancer	GXF 251 L	0.03	
						Human lung cancer	LXF 1121 L	0.38	
							LXF 289 L	0.43	
							LXF 526 L	0.43	
							LXF 529 L	0.08	
							LXF 629 L	0.04	
							NCI-H460	0.31	
						Human breast cancer	MAXF 401NL	0.01	
							MCF-7	0.12	
						Human skin cancer	MEXF 276 L	0.05	
							MEXF 394NL	0.28	
							MEXF 462NL	0.06	
							MEXF 514 L	0.38	
							MEXF 520 L	0.32	
						Human ovarian cancer	OVXF 1619 L	0.26	
							OVXF 899 L	0.08	
							OVXF OVCAR3	0.02	
						Human pancreatic cancer	PAXF 1657 L	0.03	
							PANC1	0.33	
						Human prostate cancer	PRXF 22RV1	0.03	
							DU145	0.75	
							LN-caP	0.94	
							PRXF PC3M	0.02	
						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_{50} (µg/ml)	Ref.
							RXF 393NL	0.08	
							RXF 486 L	0.03	
							RXF 944 L	0.32	
						Human uterus cancer	UXF 1138 L	0.03	
19	*Petrosia* sp.	*A. versicolor*	Malt extract, glucose, peptone, and seawater	Mycelia and medium	Fellutamide C	Human lung cancer	A-549	18.44	(Lee, *et al.*, 2010a)
						Human ovarian cancer	SK-OV-3	13.26	
						Human skin cancer	SK-MEL-2	2.84	
						Human CNS cancer	XF-498	2.17	
						Human colon cancer	HCT-15	1.73	
20	*Petrosia* sp.	*A. versicolor*	Malt extract, glucose, peptone, and seawater	Mycelia and medium	Methyl averantin	Human lung cancer	A-549	0.64	(Lee, *et al.*, 2010b)
						Human ovarian cancer	SK-OV-3	1.17	
						Human skin cancer	SK-MEL-2	1.10	
						Human CNS cancer	XF-498	0.41	
						Human colon cancer	HCT-15	0.49	
21	*Pseudoceratina purpurea*	*Tritirachium* sp. SpB081112MEf2	Brown rice, yeast extract, Na-tartrate, KH_2PO_4, and water	Mycelia and medium	JBIR-97	Human cervix cancer	HeLa	6.78	(Ueda *et al.*, 2010)
						Human mesothelioma	ACC-MESO-1	19.10	
					JBIR-98	Human cervix cancer	HeLa	10.47	
						Human mesothelioma	ACC-MESO-1	38.82	
					JBIR-99	Human cervix cancer	HeLa	10.47	
						Human mesothelioma	ACC-MESO-1	36.35	
22	*Callyspongia* sp. cf. C. flammea	*Stachylidium* sp.	Biomalt, sea salt, and water	Mycelia and medium	Marilones C	Human lung cancer	NCI-H460	10.23	(Almeida *et al.*, 2011)
						Human breast cancer	MCF-7	6.60	
						Human glioblastoma	SF-268	9.54	
23	*Psammocinia* sp.	*Aspergillus insuetus*	Potato, dextrose, and water	Medium	Insuetolide C	Human leukemia	MOLT-4	5.00 x 10^4	(Cohen *et al.*, 2011)
24	*G. cydonium*	*Arthrinium* sp.	Barley, spelt whole grain flakes, soy peptone, $MnCl_2$, and water	Mycelia and medium	Anomalin A	Mouse lymphoma	L5178Y	0.11	(Ebada *et al.*, 2011)
						Human ovarian cancer	A2780	1.19	
						Human ovarian cancer	A2780CisR	7.13	
25	*Petrosia* sp.	*A. versicolor*	Malt extract, glucose, peptone, and seawater	Mycelia and medium	Fellutamide F	Human lung cancer	A-549	1.81	(Lee *et al.*, 2011)
						Human ovarian cancer	SK-OV-3	1.20	
						Human skin cancer	SK-MEL-2	0.67	
						Human CNS cancer	XF-498	0.14	
						Human colon cancer	HCT-15	0.13	
26	*Stelletta* sp.	*Penicillium* sp. (J05B-3-F-1)	Malt extract, glucose, peptone, and seawater	Mycelia and medium	(3S)-Hexylitaconic acid	Human lung cancer	A-549	> 30.00	(Li *et al.*, 2011)
						Human ovarian cancer	SK-OV-3	> 30.00	
						Human skin cancer	SK-MEL-2	> 30.00	
						Human cns cancer	XF-498	> 30.00	
						Human colon cancer	HCT-15	> 30.00	
27	*Suberites domuncula*	*A. ustus* strain 8009	Barley, spelt whole grain flakes, soy peptone, $MnCl_2$, and water	Mycelia and medium	Aspergillamide A	Mouse lymphoma	L5178Y	> 10.00	(Liu *et al.*, 2011)
					Aspergillamide B			> 10.00	
28	*Xestospongia testudinaria*	*Aspergillus* sp.	Glucose, yeast extract, peptone, and seawater	Medium	Aspergiterpenoid A	Human leukemia	HL-60	> 50.00	(Li *et al.*, 2012)
						Human lung cancer	A-549	> 50.00	
29	*Xestospongia testudinaria*	*Aspergillus* sp.	Glucose, yeast extract, peptone, and seawater	Medium	Disydonol A	Human liver cancer	HepG-2	9.31	(Sun *et al.*, 2012)
						Human cervix cancer	Ca Ski	12.40	
					Disydonol C	Human liver cancer	HepG-2	2.91	
						Human cervix cancer	Ca Ski	10.20	

No.	Sponge species	Fungi association	Fermentation medium	Extraction specimen	Compound	Cancer type	Cell line	IC_{50} (µg/ml)	Ref.
30	Unidentified marine sponge CRI282	*Aspergillus unguis* CRI282-03	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-dimethyldibenzo[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	Mouse leukemia	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_2PO_4, $MgSO_4$, 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	Huh-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	HepG-2	3.65	
						Human gastric cancer	BGC-823	1.76	
						Human lung cancer	NCI-H1650	1.18	
						Human ovarian cancer	A2780	4.16	
38	Unidentified Marine Sponge	*Alternaria* sp. SP-32	Sorbitol, maltose, MSG, KH_2PO_4, $MgSO_4$, 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_2PO_4, MgSO4, 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	Tandyukisin E	Mouse leukemia	P338	2.17	(Suzue *et al.*, 2016)
						Mouse leukemia	HL-60	2.22	
						Mouse leukemia	L1210	3.59	
42	*Cinachyrella australiersls*	*Aspergillus insulicola* MD10-2	Glucose, peptone, KH_2PO_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* XS-20090017	Rice, sea salt, and water	Mycelia and medium	Corynesidone A	Human cervix cancer	HeLa	4.14	(Zhao *et al.*, 2016a)
					Corynethers A	Human leukemia	HL-60	9.25	
44	*Neopetrosia chaliniformis* AR-01	*Aspergillus nomius*	Rice and water	Mycelia and medium	Extract	Human colon cancer	WiDr	> 100	(Artasasta *et al.*, 2017)
45	*P. foliascens*	*F. lateritium* 2016F18-1	Glucose, peptone, yeast extract, $CaCO_3$, and seawater	Medium	Pyripyropene O	Human nasopharyngeal cancer	CNE1	1.27	(Cao *et al.*, 2017)
						Human nasopharyngeal cancer	CNE2	1.63	
						Human nasopharyngeal cancer	HONE1	3.26	
						Human nasopharyngeal cancer	SUNE1	0.51	
						Human cervix cancer	GLC82	4.38	
						Normal cell	HL7702	1.88	
46	*Sarcotragus muscarum*	*Arthrinium* sp.	Rice and water	Mycelia and medium	Spiroarthinols A	Human colon cancer	Caco-2	n.a.	(Elissawy *et al.*, 2017)
					Spiroarthinols B			n.a.	
47	*Axinella cannabina*	*Talaromyces rugulosus*	Rice, sea salt, and water	Mycelia and medium	Talarodilactone A	Mouse lymphoma	L5178Y	2.33	(Küppers *et al.*, 2017)
					Talarodilactone B			0.76	
48	*P. fusca*	*P. heterocornis*	Rice, artificial sea salt, and water	Mycelia and medium	Pestalachloride B	Human gastric cancer	BCG-823	2.77	(Lei *et al.*, 2017b)
						Human lung cancer	NCI-H460	9.63	
						Human prostate cancer	PC-3	11.47	
						Human cervix cancer	SMMC-7721	3.22	
49	*P. fusca*	*P. heterocornis*	Rice, artificial sea salt, and water	Mycelia and medium	Heterocornol A	Human gastric cancer	BCG-823	7.37	(Lei *et al.*, 2017a)
						Human lung cancer	NCI-H460	8.36	
						Human prostate cancer	PC-3	12.28	
						Human cervix cancer	SMMC-7721	5.92	
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)
						Human liver cancer	HepG-2	0.56	
						Human gastric cancer	BGC-823	> 2.66	
						Human lung cancer	NCI-H1655	0.69	
						Human ovarian cancer	A2780	0.55	
51	*Stelletta* sp.	*Aspergillus sydowii* J05B-7F-4	Glucose, malt extract, peptone, and seawater	Mycelia and medium	Diorcinolic acid	Human nasopharyngeal cancer	KB	23.41	(Liu *et al.*, 2017)
						Human colon cancer	HCT-116	17.74	
						Human liver cancer	HepG-2	21.73	

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)
						Human breast cancer	T47D	270.00	
53	*Niphates* sp.	*H. sinuosae*	Rice and artificial seawater	Mycelia and medium	Hansfordiol A	Human colon cancer	HCT-8	n.a.	(Wu *et al*., 2017)
						Human liver cancer	BEL-7402	n.a.	
						Human gastric cancer	BGC-823	n.a.	
						Human lung cancer	A-549	n.a.	
						Human ovarian cancer	A2780	n.a.	
54	*H. okadai*	*T. harzianum* OUPS-111D-4	Glucose, malt extract, peptone, and artificial seawater	Medium	Trichodermanin C	Mouse leukemia	P338	2.53	(Yamada *et al*., 2017)
						Human leukemia	HL-60	2.18	
						Mouse leukemia	L1210	2.43	
55	*Epipolasis* sp.	*Aspergillus candidus* KUFA0062	Rice and water	Mycelia	Preussin C	Human liver cancer	HepG-2	46.52	(Buttachon *et al*., 2018)
						Human colon cancer	HT-29	17.35	
						Human colon cancer	HCT-116	37.85	
						Human lung cancer	A-549	65.41	
						Human skin cancer	A375	45.03	
						Human breast cancer	MCF-7	39.06	
						Human glioblastoma	U251	39.00	
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)
						Human CNS cancer	XF-498	n.a.	
						Human colon cancer	HCT-15	n.a.	
						Human liver cancer	HepG-2	n.a.	
						Human breast cancer	MCF-7	n.a.	
57	*Haliclona fascigera*	*Trichophyton* sp. (WR2)	Glucose, malt extract, peptone, and seawater	Mycelia and medium	Extract	Human colon cancer	WiDr	193.95	(Handayani *et al*., 2018)
						Human breast cancer	T47D	5861.67	
						Human cervix cancer	HeLa	211.55	
						Normal cell	Vero	357.49	
		Aspergillus sp. (WR4)	Glucose, malt extract, peptone, and seawater	Mycelia and medium	Extract	Human colon cancer	WiDr	38.21	
						Human breast cancer	T47D	328.23	
						Human cervix cancer	HeLa	598.89	
						Normal cell	Vero	321.54	
		Trichophyton 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.	*Nocardiopsis* sp. UR67	Dextrose, malt extract, peptone, yeast extract, and artificial seawater	Medium	Nocartiodite A	Human myeloma	MM.1S	6.15	(Ibrahim *et al*., 2018)
						Human cervix cancer	HeLa	8.46	
						Human colon cancer	CT26	9.23	
59	*Agelas oroides*	*Aspergillus carneus*	Rice, sea salt, and water	Mycelia and medium	Isopropylchaetominine	Mouse lymphoma	L5178Y	0.18	(Özkaya *et al*., 2018)
					sterigmatocystin			0.10	
60	*Callyspongia* sp.	*Alternaria alternata* strain SCAU091	Rice, sea salt, and water	Mycelia and medium	Altertoxin VII	Human leukemia	K562	26.58	(Pang *et al*., 2018)
						Human gastric cancer	SGC-7901	8.75	
						Human liver cancer	BEL-7402	13.11	
61	*Stylissa flabelliformis*	*T. reesei* strain TV221	Dextrose, peptone, and seawater	Medium	Extract	Human colon cancer	WiDr	88.88	(Setyowati *et al*., 2018)
						Mouse mammary cancer	4T1	145.98	

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_2PO_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	MCF-7	3.03	
						Human lung cancer	A-549	5.10	
						Human liver 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. ZSDS1-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	Misszrtine A	Human liver cancer	HepG-2	n.a.	(Zhou *et al*., 2018)
						Human leukemia	HL-60	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	
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	> 16.51	
						Human cervix cancer	HeLa	> 16.51	
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_{50} (µg/ml)	Ref.
72	*Hymeniacidon* sp.	*Aspergillus* sp. NBUF87	Rice, sea salt, and water	Mycelia	Aspergimarins A	Human leukemia	CCRF-CEM	> 13.30	(Huang, *et al*., 2019a)
						Human breast cancer	MDA-MB-231	> 13.30	
						Human colon cancer	HCT-116	> 13.30	
						Human gastric cancer	AGS	> 13.30	
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)
						Human liver cancer	HepG-2	11.00	
						Human kidney cancer	786-O	5.79	
74	*Haliclona* sp.	*Aspergillus* sp. LS34	Potato, dextrose, sea salt, water	Medium	Asperther A	Human leukemia	CCRF-CEM	7.46	(Li *et al*., 2019)
						Human leukemia	K562	11.07	
			Rice, and seawater	Mycelia	Oxalicumone A	Human leukemia	CCRF-CEM	0.52	
						Human leukemia	K562	4.49	
75	*P. fusca*	*A. sydowii* SCSIO41301	Mannitol, maltose, glucose, MSG, KH_2PO_4, $MgSO_4$, yeast extract, and water	Medium	Aspergillusene D	Human leukemia	K562	n.a.	(Liu *et al*., 2019)
						Human liver cancer	BEL-7042	n.a.	
						Human gastric cancer	SGC-7901	n.a.	
						Human lung cancer	A-549	n.a.	
						Human cervix cancer	HeLa	n.a.	
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)
					Aspergillamide A			n.a.	
					Terretrione B			n.a.	
					Brevianamide F			n.a.	
					Questin			n.a.	
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)
						Human kidney cancer	OS-RC-2	13.09	
						Human kidney cancer	786-O	17.66	
78	*Callyspongia* sp.	*A. versicolor* SCSIO 41013	Rice, sea salt, and water	Mycelia	Versispiroketal A	Human glioblastoma	SF-268	26.08	(Salendra, *et al.,* 2019b)
						Human breast cancer	MCF-7	29.86	
						Human liver cancer	HepG-2	23.79	
						Human lung cancer	A-549	27.06	
79	*Callyspongia* sp.	*P. citrinum* SCSIO 41017	Rice, sea salt, and water	Mycelia	Xerucitrinic acid A	Human glioblastoma	SF-268	4.95	(Salendra, *et al*., 2019a)
						Human breast cancer	MCF-7	3.93	
						Human liver cancer	HepG-2	6.66	
						Human lung cancer	A-549	13.52	
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)
						Human leukemia	HL-60	11.41	
						Mouse leukemia	L1210	11.04	
81	*Haliclona fascigera*	*Cochliobolus geniculatus* WR12	Rice and water	Mycelia	Radicinin	Human colon cancer	WiDr	47.17	(Handayani, *et al*., 2020b)
						Human breast cancer	T47D	25.01	
						Human cervix cancer	HeLa	55.25	
						Normal cell	Vero	57.13	
82	*Chelonaplysilla* sp.	*Aspergillus flavus*	Rice and water	Mycelia	Extract	Human breast cancer	T47D	743.42	(Handayani, *et al*., 2020a)
		Phomapsis sp.	Rice and water	Mycelia	Extract			83.96	
		Beauveria bassiana	Rice and water	Mycelia	Extract			670.75	
		Aspergillus mellinus	Rice and water	Mycelia	Extract			637.24	

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 lixii* 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_2PO_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 lung cancer	H1975	3.09	
						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	
86	*Callyspongia* sp.	*Alternaria* sp. JJY-32	Potato, dextrose, and water	Mycelia and medium	Tricycloalternarenes X	Human leukemia	HL-60	2.59	(Wang *et al.*, 2020b)
						Human cervix cancer	HO8910	6.99	

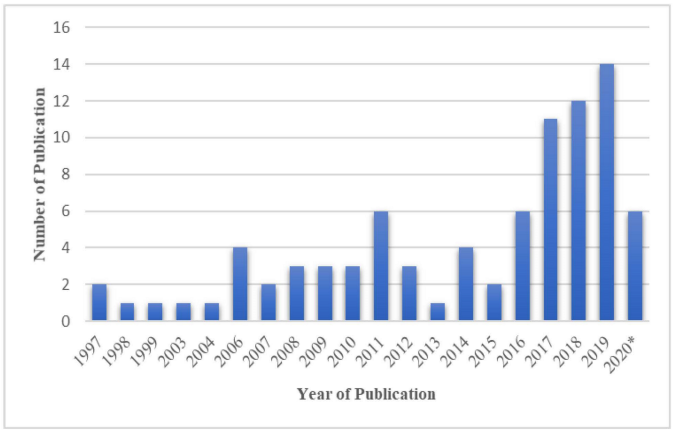

Figure 1. Distribution of conducted studies about cytotoxic activity of marine sponge-derived fungi. *June 2020.

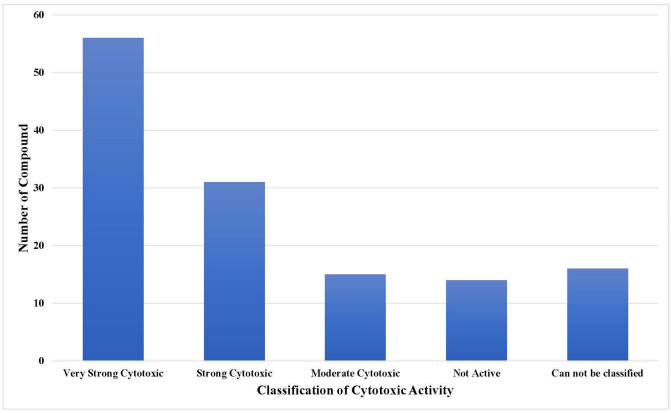

Figure 2. Classification of the component activity according to their IC_{50} values.

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; Weerapreeyakul *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,

Table 2. List of compounds with very strong cytotoxic activity based on the IC_{50} value.

No.	Compound	Cell line cancers
1	4,6-Dimethoxy-2,9-dimethyldibenzo[b,e][1,4] dioxine-1,7-diol	HL-60
2	4-O-Methylcandidusin A	A-549; DU145; H1975; HL-60; K562; MCF-7; MDA-MB-231; MV4-11; U251
3	Anomalin A	A2780; A2780CisR; L5178Y
4	Aspergillides A	L1210
5	Aspergillides C	L1211
6	Asperther A	CCRF-CEM
7	Bromophilone 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-3161	L5178Y
12	Cytochalasin K	A-549; H1975; HL-60; Huh-7; K562; MOLT-4
13	Dankastatin C	P338
14	Dankasterone	P338
15	Dankasterones A	P338
16	Dankasterones B	P338
17	Diorcinols L	A-549; DU145; H1975; HeLa; HL60; Huh-7; MCF-7
18	Disydonol C	HepG-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 L; MEXF 394NL; MEXF 462NL; MEXF 514 L; MEXF 520 L; NCI-H460; OVXF 1619 L; OVXF 899 L; OVXF OVCAR3; PANC1; PAXF 1657 L; PRXF 22RV1; PRXF PC3M; PXF 1752 L; RXF 1781 L; RXF 393NL; RXF 486 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	Heterocornol A	BCG-823; NCI-H460; SMMC-7721
33	Heterocornols O	786-O; 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 averantin	A-549; HCT-15; SK-MEL-2; SK-OV-3; XF-498
39	Nocartiodite A	CT26; HeLa; MM.1S

No.	Compound	Cell line cancers
40	Ophiobolin H	L5178Y
41	Oryzamides B	HeLa
42	Oxalicumone A	CCRF-CEM; K562
43	Pestalachloride B	BCG-823; NCI-H460; SMMC-7721
44	Pyripyropene O	CNE1; CNE2; GLC82; HL7702; HONE1; SUNE1
45	Sterigmatocystin	L5178Y
46	Talarodilactone A	L5178Y
47	Talarodilactone B	L5178Y
48	Tandyukisin E	HL-60; L1210; P338
49	Trichodenone A	P338
50	Trichodenone B	P338
51	Trichodenone C	P338
52	Trichodermanin C	HL-60; L1210; P338
53	Trichoharzin	HL-60; L1210; P338
54	Tricycloalternarenes X	HL-60; HO8910
55	Varioxiranol K	A2780; BGC-823; HCT-116; HepG-2; NCI-H1650
56	Xerucitrinic acid A	HepG-2; MCF-7; SF-268

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-Lateff *et al*., 2003; Ebada *et al*., 2011; Morel *et al*., 2000; Peres *et al*., 2000).

Bioactive polyketide derivatives include bromophilone A **(2)**, epoxyphomalin 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. Epoxyphomalin A **(6)** derived from the fungus *Phoma* sp. associated with the sponge *Ectyplasia 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*, *Hyposylon*, *Xylaria*, *Daldinia*, *Pseudeurotium*, 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

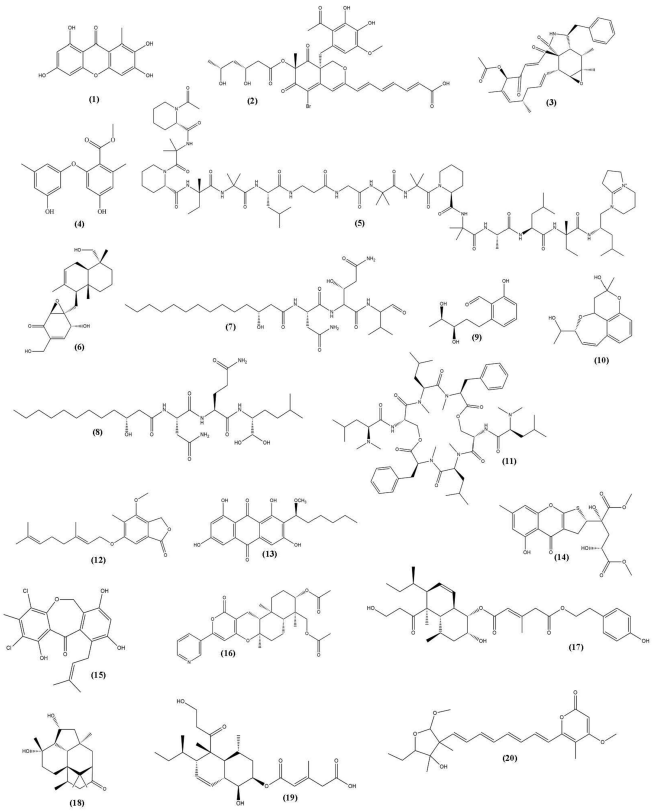

Figure 3. Structure of a very strong cytotoxic component (Almeida *et al*., 2011; Boot *et al*., 2006; Cao *et al*., 2017; Cruz *et al*., 2006; Ebada *et al*., 2011; Frank *et al*., 2019; Lee et al., 2010a, 2010b, 2011; Lei et al., 2017a, 2017b, 2019; Li *et al*., 2019; Mohamed *et al*., 2009; Suzue *et al*., 2016; Tian *et al*., 2018a; Wang *et al*., 2015; Wu *et al*., 2015; Yamada et al., 2014, 2017).

a cell without a nucleus (Liu *et al*., 2006; Wang *et al*., 2015). Diorcinols L **(4)** is a phenol derivative metabolite (Fig. 3). This metabolite comes from the fungus *Didymellaceae* sp. SCSIO F46 in association with *Callyspongia* 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 peptaibiotic 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 (Boot *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 *Petrosia* 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, antiangina 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*. *Stachylidium* sp. are associated with the sponge *Callyspongia* sp. cf. *C. flammea* producing marilone C **(12)** components included in the phthalides group (Fig. 3) (Almeida *et al*., 2011).

Aspergillus versicolor associated with the sponge *Petrosia* 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 IC_{50} 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 IC_{50} ranging from 2 to 10 µg/ml in cancer cell lines BCG-823, NCI-H460, and SMMC-7721 (Fig. 3) (Lei *et al*., 2017b; Li *et al*., 2008). Pyripyropene O **(16)** and trichodermanin C **(18)** are components belonging to the terpenes group (Fig. 3). Pyripyropene O **(16)** is pyripyropenes derived from sesquiterpenes conjugated with a-pyrone and pyridine moieties. Pyripyropenes are representative metabolites of several genera of fungi, such as *Aspergillus* and *Penicillium*. The bioactive metabolite pyripyropene O **(16)** is derived from *Fusarium lateritium* 2016F18-1 which is associated with the sponge *Phyllospongia foliascens*. Trichodermanin 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 decalin skeleton have various bioactivities, such as antibacterial, antifungal, and phytotoxicity. There are many decalin 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 IC_{50} values of 2.22, 3.59, and 2.17 µg/ml, respectively. Trichoharzin **(19)** is a polyketide constructed with an alkylated decalin skeleton and esterified with 3-methylglutaconic acid, a rare acyl moiety. This bioactive metabolite has cytotoxic activity in cell line HL-60 with IC_{50} = 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, HCT-116, HepG-2, and NCI-H1650 with an IC_{50} 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 *Culcitalna achraspora* Meyers and Moore, *Humicola alopallonella* Meyers and Moore, *Orbomyces spectabilis* Linder, *Halosphaeria mediosetigera* 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%–1.5% (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), $NaNO_3$ (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 $NaNO_3$ and NH_4Cl (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 *Paecilomyces* (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 fungi 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 KH_2PO_4, $MgSO_4$, $MnCl_2$, 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, cyclodepsipeptides, 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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