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Review Article

Mangrove-Derived Fungi as a Reservoir of Bioactive Secondary Metabolites Promising for Anticancer Leads: A Literature Review

Jamur dari Mangrove sebagai Sumber Senyawa Metabolit Sekunder Bioaktif yang Berpotensi sebagai Kandidat Antikanker: Review Literatur

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Abstract

Cancer was the leading cause of death, which accounting for nearly 10 million deaths globally in 2020. Currently, cancer treatment still relies on chemotherapy, however, most anticancer drugs showed non-specific toxicity to normal cell proliferation resulting in various side effects, and are ineffective against many forms of cancer. In addition, the increasing case of chemoresistance of cancer cells to chemotherapy has boosted the discovery of new anticancer agents. Natural products are known as the origin of several clinically used anticancer agents, *e.g.* taxol and vincristine. Among natural products, mangrove-derived fungi are of particular scientific interest evidenced by the increasing rate of publications on cytotoxic secondary metabolites reported. Hence, this literature review aims to provide comprehensive information on cytotoxic secondary metabolites isolated from mangrove-derived fungi, which might contribute to the search for anticancer leads from natural resources. Data were collected from original research articles published on scientific-based sources such as Google Scholar, PubMed, Taylor and Francis, Elsevier, and MDPI, in the range of 2011-2022. Fifty-four cytotoxic secondary metabolites with IC_{50} values below 10 µM were described herein, which were classified in to 8 groups of metabolites. These compounds were reported from 16 genera of mangrove-associated fungi. Among them, *Aspergillus* and *Penicillium* were the most frequent producers of cytotoxic metabolites, suggesting their enormous potential as a source of pharmacophores for anticancer candidates.

Abstrak

Kanker merupakan penyebab utama kematian di seluruh dunia, terhitung hampir 10 juta kematian pada tahun 2020. Saat ini pengobatan kanker masih mengandalkan kemoterapi, namun sebagian besar obat antikanker menunjukkan toksisitas nonspesifik terhadap proliferasi sel normal yang mengakibatkan berbagai efek samping, dan tidak efektif terhadap berbagai bentuk kanker. Selain itu, meningkatnya kasus kemoresistensi sel kanker terhadap kemoterapi telah mendorong penemuan agen antikanker baru. Bahan alam dikenal sebagai asal dari beberapa agen antikanker yang digunakan secara klinis, seperti taxol dan vinkristin. Di antara bahan alam, jamur yang berasal dari mangrove telah menarik minat peneliti yang dibuktikan dengan meningkatnya jumlah publikasi metabolit sekunder sitotoksik yang dilaporkan. Artikel review ini bertujuan untuk menyediakan informasi secara komprehensif tentang metabolit sekunder sitotoksik yang dihasilkan oleh jamur yang berasal dari mangrove, dalam upaya penemuan senyawa penuntun antikanker dari bahan alam. Data dikumpulkan dari artikel penelitian yang dipublikasikan pada sumber ilmiah seperti Google Scholar, PubMed, Taylor and Francis, Elsevier, dan MDPI, dalam rentang tahun 2011-2022. Lima puluh empat metabolit sekunder sitotoksik dengan nilai IC_{50} di bawah 10 µM diuraikan dalam artikel ini, yang diklasifikasikan menjadi 8 kelompok metabolit. Senyawa-senyawa tersebut dilaporkan dari 16 genera jamur yang berasosiasi dengan mangrove. *Aspergillus* dan *Penicillium* adalah penghasil metabolit sitotoksik yang paling sering dilaporkan dan menunjukkan potensi besar sebagai sumber farmakofor untuk kandidat antikanker.

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INTRODUCTION

Cancer is a rising burden on global health and one of the leading causes of death. Cancer is characterized by the growth and spread of abnormal and uncontrolled cells.[1] In 2020, the prevalence of cancer new cases reached more than 19 million cases,

with more than 9.9 million people died from cancer globally.[2] That number is projected to multiply to approximately 37 million new cancer cases by 2040.[3] Due to this fact, cancer is considered one of the life-threatening diseases that demand to be addressed immediately.

Currently, cancer therapy still relies on drugs, molecular biology, and immune-mediated therapy. However, thus far, no level of therapy can reduce cancer mortality.[1] In addition, many anticancer drugs show nonspecific toxicity to normal cell proliferation, various side effects, and are not effective against many forms of cancer.[4] Therefore, novel anticancer agents are urgently needed as an effort to control the death rate apart from several types of therapy that have been carried out for cancer cells.

Natural products, especially plant-derived compounds, have been widely studied and researched due to their promising bioactivity. For cancer therapy, 60% of anticancer candidates derived from natural products showed significant efficacy in clinical use. Thus, natural products are taken into account as favorable lead compounds for the development of new drug candidates.[5] Other broadly investigated reservoirs of bioactive natural products is endophytic fungi. Endophytic fungi are recognized as productive sources for the discovery of interesting structures and biologically active metabolites.[6,7] Among the fungi of plant origin, those associated with mangroves have received much attention from scientists due to their unique ecosystem.[8] Situated in intertidal zones, mangroves are exposed to eclectic environmental conditions; creating a vast range of substrata that allow endophytic fungi to differentiate their ecological niche.[9] Hence, mangrove is considered a treasure chest reserving a diverse endophytic fungal community.[10]

Marine-derived fungi, including those isolated from mangrove habitat provide a wide variety of bioactive secondary metabolites with unique structures, belonging to alkaloids, benzopyrones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, and others that can act as anticancer agents.[4] Therefore, the aim of this review is to provide comprehensive information on cytotoxic natural products produced by mangrove-derived fungi, which possibly could contribute to the discovery of anticancer leads from natural resources. Herein, we describe secondary metabolites isolated from mangrove-derived fungi, reported in the last 10 years (2011-2022) for their cytotoxicity against various cancer cells. As we intended to focus on promising cytotoxic secondary metabolites promising for anticancer leads, we restricted our review to cytotoxic compounds having IC_{50} values below 10 µM.

METHOD

The search for scientific articles utilized various databases such as Google Scholar, PubMed, Taylor and Francis Online, Elsevier, and MDPI. Specific keywords, such as "mangrove-derived fungi," "anticancer," "fungi of mangrove," "cancer cell inhibitor," and "cytotoxic," were employed during the search. As a primary screening of relevant publications, only original research papers regarding anticancer metabolites produced by mangrove-associated fungi from international journals published between 2011 and 2022 were screened for this literature review. The inclusion criteria were further defined to filter the scientific articles included for the review, which include only compounds isolated from mangroves-derived fungal endophytes and those exhibited IC_{50} values less than 10 µM in cytotoxicity tests. Whereas compounds from mangrove-derived fungal endophytes having IC_{50} values above 10 µM were put as exclusion criteria.

RESULTS AND DISCUSSION

Most fungal endophytes possess the capability to produce bioactive metabolites and are therefore regarded as promising natural sources of lead molecules. Fungal endophytes derived from marine habitats have been repeatedly reported for their bioactive compounds, which exert various pharmacological actions. Many of the reported natural products so far bear unique chemical structures, which can be classified into alkaloids, peptides, phenolic acids, polyketides, pyrones, quinones, steroids, or terpenoids. The production of these metabolites by mangrove-associated fungi might occur due to the symbiotic relationship that exists between endophytes and their host plants or environments which could trigger the production of

these secondary metabolites. Compounds produced by endophytic fungi associated with mangroves also can act as plant defense barriers against pathogens. Moreover, these compounds can further act as potential antivirals, antimicrobials, or cytotoxic agents among other promising pharmacological actions.

All in all, following the literature search, 32 primary research articles that specifically addressed secondary metabolites produced by mangrove-associated fungi and their potential as cytotoxic agents were included in this review, as presented in **Table 1**.

Table 1. Cytotoxicity of Secondary Metabolites Isolated From Mangrove-Derived Fungi

Compound's Group	Name of Strain	Compound	Cell lines	IC_{50} (µM)	Ref.
Quinone	*Nigrospora* sp. No. 1403	Deoxybostrycin **[1]**	MDA-MB-435 HCT-116 HepG2	3.19 5.69 9.99	12
	Phomopsis sp. (PM0409092)	Altersolanol A **[2]**	BXF 1218L	0.01	13
	Paradictyoarthrinium diffractum BCC 8704	Paradictyoarthrin B **[3]**	KB	8.27	14
	Talaromyces sp. SK-S009	6-[1-(acetyloxy)ethyl]-5-hydroxy-2,7- dimethoxy-1,4-naphthalenedione **[4]**	RAW 264.7	1.70	15
		Talanaphthoquinone A **[5]**		3.90	
		Anhydrofusarubin **[6]**		5.20	
		Javanicin **[7]**		5.60	
		5-hydroxy-6-(1-hydroxyethyl)-2,7-dimethoxy-1,4-naphtha **[8]**		7.50	
		6-[1-(acetyloxy)ethyl]-5-hydroxy-2,7- dimethoxy-1,4-naphthalenedione **[9]**		7.70	
Polyketide	*Phomosis* sp. A818	Mycoepoxydiene **[10]**	MDA-MB-435	7.85	18
	Trichoderma sp. 307	Botryorhodine H **[11]**	MMQ GH3	3.09 3.64	18
	Cytospora sp.	Integracin A **[12]** Integracin B **[13]**	HepG2	5.98 9.97	19
	Pseudopestalotiopsis theae MN814071	Cytosporin W **[14]**	L5178Y	3.00	20
	Penicillium sp. HS-N-27	Brefeldin A **[15]**	A549 HeLa HepG2	0.10 0.20 0.20	22
Phenol	*Penicillium expansum* 091 006 Endogenous	Expansol B **[16]**	HL-60	5.40	25
	Alternaria sp. R6	Resveratrodehyde A **[17]**	HCT-116 MDA-MB-435	7.82 8.56	26
		Resveratrodehyde B **[18]**	HCT-116 MDA-MB-435	6.93 7.68	
	Penicillium citrinum	(-)-4-O-(4-O-β-D-glucopyranosylcaffeoyl)quinic acid **[19]**	KBvin	2.13	27
	Lasiodiplodia theobromae ZJ-HQ1	Preussomerin F **[20]**	MCF-7 HepG2 A549	3.10 3.60 7.70	28
		Preussomerin G **[21]**	MCF-7 A549 HepG2	4.20 6.20 8.50	
		Preussomerin H **[22]**	MCF-7	2.60	

Compound's Group	Name of Strain	Compound	Cell lines	IC_{50} (μM)	Ref.
			HepG2	4.40	
			A549	9.40	
		Preussomerin K **[23]**	MCF-7	2.50	
			HepG2	3.80	
			A549	5.40	
		Chloropreussomerin A **[24]**	HEK293T	4.80	
			MCF-7	5.90	
			A549	8.50	
		Chloropreussomerin B **[25]**	MCF-7	6.20	
			HepG2	7.70	
			A549	8.90	
	Aspergillus versicolor HDN11-84	Arugosin K **[26]**	HeLa	9.2	29
	Aspergillus versicolor HDN1009	Versixanthone N **[27]**	HL-60	1.70	30
			K562	2.70	
			H1975	8.50	
			MGC803	8.80	
			HO-8910	9.10	
		Versixanthone O **[28]**	HL-60	1.80	
			H1975	6.70	
			K562	8.10	
			MGC803	8.50	
Peptide	*Bionectria ochroleuca*	Pullularin A **[29]**		3.35	32
		Pullularin C **[30]**	L5178Y	8.79	
		Pullularin E **[31]**		7.36	
	Aspergillus terreus (No. GX7-3B)	Beauvericin **[32]**	A549	0.82	33
			KB	1.10	
			HeLa	1.14	
			MCF-7	2.02	
	Penicillium janthinellum HDN13-309	Trichodermamide B **[33]**	MGC803	1.60	34
			HL-60	1.80	
			HO-8910	1.90	
			K562	8.00	
	Phaeosphaeriopsis sp. S296	Phaeosphamide A **[34]**	AGS	5.14	35
Alkaloid	*Aspergillus* sp. FSY-01	Neoaspergillic acid **[35]**	K562	8.00	37
	Aspergillus sp. FSW-02		SGC-7901	8.20	
	Bionectria ochroleuca	Verticillin D **[36]**	L5178Y	<0.10	32
	Penicillium sp. GD6	Meleagrin **[37]**	A549	8.30	38
			HL60	9.70	
	Penicillium chrysogenum V11	Cytoglobosin C **[38]**	A549	3.35	39
			SGC-7901	8.15	
		Chaetoglobosin A **[39]**	A549	6.56	
			SGC-7901	7.48	
		Penochalasin I **[40]**	SGC-7901	7.32	
			MDA-MB-435	7.55	
	Chaetomium globosum kz-19	Chaetoglobosin C **[41]**	A549	7.60	21
		Chaetoglobosin E **[42]**	HeLa	7.50	
		Chaetoglobosin G **[43]**	HeLa	3.70	
			A549	7.30	
		Chaetoglobosin V **[44]**	HeLa	3.80	
		Phychaetoglobin D **[45]**	HeLa	9.20	
	Phomopsis asparagi DHS-48	Phomoparagin D **[46]**	HeLa	5.82	23
Pyrone	*Aspergillus* sp. HN15-5D	Aspergisocoumrin A **[47]**	MDA-MB-435	5.08	40
		Aspergisocoumrin B **[48]**		4.98	

Compound's Group	Name of Strain	Compound	Cell lines	IC_{50} (μM)	Ref.
	Fusarium sp. 2ST2	4H-1-benzopyran-4-one-2,3-dihydro-5-hydroxy-8-(hydroxylmethyl)-2-methyl **[49]**	MDA-MB-435 A549	3.80 5.60	41
		Fusarisetin E **[50]**	A549	8.70	
		Fusarisetin F **[51]**		4.30	
Fluoranthene Terpenoid	*Annulohypoxylon* sp	Daldinone I **[52]**	Ramos	6.60	42
	Aspergillus terreus (No. GX7-3B)	3β,5α-dihydroxy-(22E,24R)-ergosta-7,22-dien-6-one **[53]**	HeLa KB A549 MCF-7	0.68 1.50 1.95 4.98	33
	Aspergillus candidus MK209104	Asperterphenyllin G **[54]**	A549 SH-SY5Y HCT-116 U87 MGC-803 HO8910 HeLa L-02 BEL-7402	0.40 0.60 0.80 0.90 1.00 1.30 1.70 1.70 6.00	16

The search yielded a total of 54 compounds from across 16 fungal genera, categorized into eight compound groups. Notably, most of the anticancer compounds belonged to the phenol, polyketide, and quinone groups (**Figure 1**).

Quinones

Quinones are colored compounds with a basic benzoquinone chromophore consisting of two carbonyl groups with two double bonds. Coloring quinones are a system of benzoic quinone rings that are fused with sufficient conjugation to achieve color. Quinones are a class of aromatic compounds that are abundant in nature and can be found in several fungal families, especially in mangrove-derived fungi.[11]

Chemical investigation on endophytic fungi from *Nigospora* species, namely *Nigrospora* sp. No. 1403 isolated from unidentified mangrove in the South China Sea, led to the isolation of deoxybostrycin **[1]**. Based on cytotoxic in vitro tests, compound **[1]** showed strong cytotoxicity against MDA-MB-435, HepG2, and HCT-116 with IC_{50} values of 3.19, 5.69, and 9.99 μM, respectively.[12] Furthermore, chromatographic work-up on *Phomopsis* sp. (PM0409092) associated with the leaves of *Nyctanthes arbor-tristis* produced altersolanol A **[2]** that showed remarkable cytotoxicity towards bladder cancer cells BXF 1218L with IC_{50} of 0.01 μM.[13] Another fungal endophyte, *Paradictyoarthrinium diffractum* BCC 8704 isolated from unidentified mangrove collected from Ranong Province, Thailand, produced paradictyoarthrin B **[3]** which showed cytotoxicity against epidermoid carcinoma KB cells with IC_{50} values of 9.22 μM.[14]

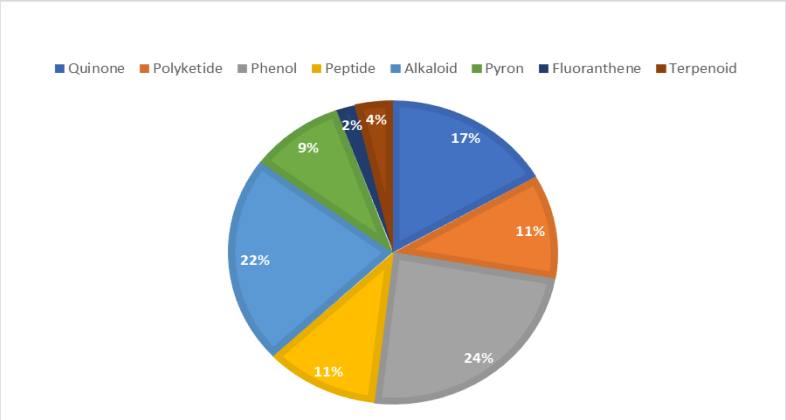

Figure 1. Cytotoxic secondary metabolites produced by various species of mangrove-associated fungi.

Talaromyces sp. SK-S009, an endophyte residing in the fresh fruit of *Kandelia obovata,* produced naphthoquinone derivatives that showed promising cytotoxicity. These compounds, namely 6-[1-(acetyloxy)ethyl]-5-hydroxy-2,7- dimethoxy-1,4-naphthalenedione **[4]**, talanaphthoquinone A **[5]**, anhydrofusarubin **[6]**, javanicin **[7]**, 5-hydroxy-6-(1-hydroxyethyl)-2,7-dimethoxy-1,4-naphtha **[8]**, 6-ethyl-2,7-dimethoxyjuglone **[9]**, and proved to exhibit cytotoxic effect against RAW 264.7 cell lines with IC_{50} values of 1.70, 3.90, 5.20, 5.60, 7.50, and 7.70 µM, respectively.[15] The structures of the quinones group compounds are shown in **Figure 2**.

Among the quinones described herein, altersolanol A showed the most pronounced activity against bladder cancer cells and have been well studied against various cancer cells. Altersolanol A showed strong cytotoxicity against human chronic myeloid K562 leukemia and A549 lung cancer cells, while no cytotoxic effect found against non-cancer PBMC cells.[43] Anthraquinone structure with the presence of two keto groups in the central ring might have significant contribution the cytotoxic activity of the compound, as shown in altersolanol A. Many anthraquinone derivatives isolated from various natural resources such as from plant and microorganisms or synthetic are also known for their anticancer activity.[44] As an example, daunorubicin is one of the most popular among cytotoxic agents bearing anthraquinone structure. Study on structure-activity relationship of various quinone compounds will be necessary to predict the core quinone structure or the attached functional groups which significantly influenced their activity against cancer cells. Meanwhile, the cytotoxic effects may differ against different cancer cells as the sensitivity of each cancer cells against each tested compound differs.

Polyketides

Polyketides are bioactive compounds found many in fungi, bacteria, and plants, where these polyketides are known to have various biological activities, including anticancer.[17] Mycoepoxydiene **[10]** produced by *Phomosis* sp. A818 associated with *Kandelia candel* leaves, showed inhibition against breast cancer MDA-MB-435 cell lines with an IC_{50} value of 7.85 µM.[18] Another polyketide, botryorhodine H **[11]** which is reported to inhibit the growth of MMQ and GH3 cells with IC_{50} values of 3.09 and 3.64 µM, was afforded from *Trichoderma* sp. 307.[18]

The fungal strain *Cytospora* sp. isolated from the mangrove *Ceriops tagal* produced two secondary metabolites namely integracins A-B **[12, 13]** which showed inhibition on human liver cancer HepG2 cells with IC_{50} values of 5.98 and 9.97 µM, respectively.[19] The compound cytosporin W **[14]** produced by *Pseudopestalotiopsis theae* MN814071 showed inhibition of L5178Y cancer cells growth with an IC_{50} value of 3.00 µM.[20]

Brefeldin A **[15]** produced by strains of *Penicillium* sp. HS-N-27 isolated from *Acanthus ilicifolius* mangrove in the South China Sea, showed inhibition against A549, HeLa, and HepG2 cells with IC_{50} values 0.10, 0.17, and 0.23 µM.[22] Brefeldin A is among polyketides that showed pronounced cytotoxic effect against various cell lines. Brefeldin A is a well-known natural Golgi-disruptor and Arf-GEFs inhibitor, and shows strong anticancer activity in a variety of cancers. Brefeldin A is considered as a promising lead molecule for developing anticancer drugs. As the metabolites of the fungi *Penicillium* sp. (HS-N-27) are relatively simple and Brefeldin A is easily separated and purified, this provides the source of compounds for the study of the medicinal properties of Brefeldin A. The structures of the polyketide compounds are shown in **Figure 2**.

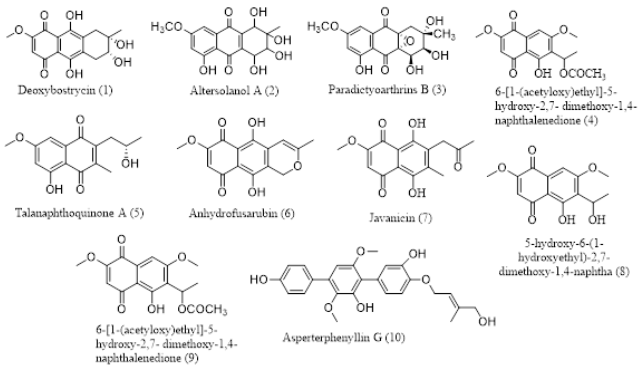

Figure 2. Chemical structures of cytotoxic quinones and polyketide from mangrove-derived fungi

Phenolic compounds

Phenolic compounds include a number of compounds having an aromatic ring with one or more hydroxyl groups and can vary from simple molecules to polymers complex. Compound antioxidant activity phenolics are directly related with a chemical structure such as degrees glycosylation and the number and position of groups hydroxyl group linked carboxyl functional. These compounds make important contributions for antioxidant activity because it has activity in binding radicals as well chelate metal.[45]

Phenolic compounds are compounds that act as antioxidants in plants. This group of compounds is rarely found in fungal species.[24] Endogenous *Penicillium expansum* 091006 strain produces

metabolites from the polyphenolic compound group, namely expansol B [**16**] which can inhibit HL-60 cancer cells with IC_{50} values of 5.40 µM.[25] Resveratrodehyde A and B **[17, 18]** are a group of resveratrol compounds produced from the fungal strain *Alternaria* sp. R6 isolated from the root of *Myoporum bontioides* A. Gray in Leizhou peninsula, Guangdong. These compounds strongly inhibited MDA-MB-435 and HCT-116 cancer cells with IC_{50} values of 8.56 and 7.82 µM **[17]**; 7.68 and 6.93 µM **[18].**[26] Substitution of one of H atom attached to the first ring (R1) in **[17]** to aldehyde group as shown in **[18]**, did not affect the activity against the tested cancer cells.

Penicillium citrinum from *Avicennia marina* collected in Fujian province, China was found to produce (-)-4-O-(4-O-β-D-glucopyranosylcaffeoyl) quinic acid **[19]** that showed cytotoxicity against KBvin cell lines with IC_{50} value of 2.13 µM.[27] An endophytic fungus namely *Lasiodiplodia theobromae* ZJ-HQ1, isolated from leaf of *Acanthus ilicifolius* in Guangdong Province, China, was identified produced preussomerin F, G, H, K **[20-23]** and chloropreussomerin A-B **[24-25]**. Compounds **[20-23]** and **[25]** have inhibitory activity against cancer cells MCF-7, HepG2, and A549 with IC_{50} value of 3.10, 3.60 and 7.70 µM **[20]**; 4.20, 8.50 and 6.20 µM **[21]**; 2.50, 4.40 and 9.40 µM **[22]**; 2.50, 3.80 and 5.40 µM **[23]**; 6.20, 7.70 and 8.90 µM **[25]**. Meanwhile, compound **[24]** has inhibitory activity against cancer cells HEK293T, MCF-7, and A549 with IC_{50} values of 4.80, 5.90, and 8.50 µM.[28]

Aspergillus versicolor HDN11-84 isolated from *Thespesia populnea* mangrove in Guangxi Province, China produced arugosin K **[26]** which inhibited HeLa cancer cells with IC_{50} values of 9.2 µM.[29] *Aspergillus versicolor* strain HDN1009 was identified to produce versixanthone N-O **[27, 28]**. Compound **[27]** inhibited HL-60, K562, H1975, MGC803, and HO-8910 with IC_{50} values of 1.70, 2.70, 8.50, 8.80, and 9.10 µM. Meanwhile, compound **[28]** inhibited HL-60, H1975, HO-8910 and MGC803 cells with IC_{50} values of 8.10, 8.50, 6.70, and 1.80 µM.[30] The structures of the phenol group compounds are shown in **Figure 3**.

Among the phenolic compounds described herein, compounds **[20-25]** showed some interesting features where the structural diversity comes from the different substitution on the first dan the fourth rings of their skeleton. It showed that the presence of epoxide ring attached to the first ring of the skeleton or the presence of a chlorine atom and hydroxyl or -methoxy group instead of epoxy did not influence their cytotoxicity as all of their activity against the tested cancer cells fall below 10 µM. Similarly, substitution of hydroxy to keto group at the fourth ring of the structure or the presence of hydroxyl or methoxy group instead of H atom or a double bond has no effect on the cytotoxicity on this type of structure.

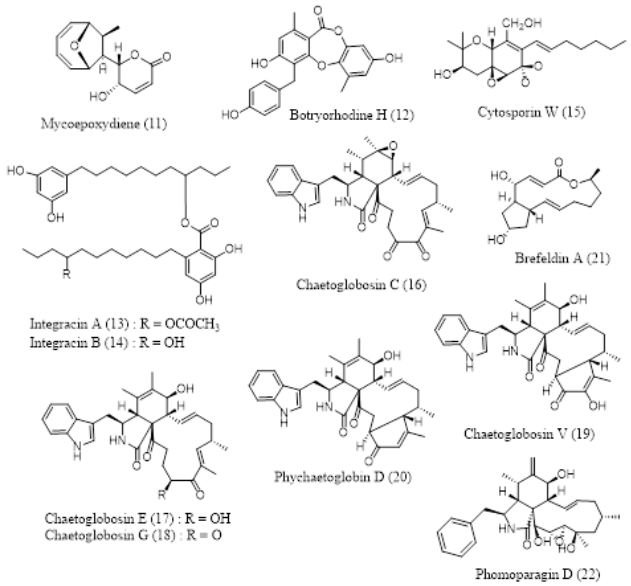

Figure 3. Chemical structures of cytotoxic phenolic from mangrove-derived fungi

Peptides

Peptides are compound consisting of two or more amino acids linked in a chain. Peptides are an important part of nature. Currently, many peptide compounds have been developed as potential source of medicinal raw materials in health and pharmaceutical.[31] The fungal strain *Bionectria ochroleuca* is known to produce three secondary metabolites belonging to the peptide group, including pullularin A, C, and E **[29,30,31]** which are known to inhibit L5178Y cancer cells with IC_{50} values of 3.35, 8.79 and 7.36 µM, respectively.[32]

Beauvericin **[32]** produced by *Aspergillus terreus* (No. GX7-3B) strain isolated from the branch of *Bruguiera gymnoihiza* (Linn.) Savigny in the South China Sea in Guangxi province showed inhibition against A549, KB, HeLa, and MCF-7 cells. with IC_{50} values of 0.82, 1.10, 1.14, and 2.02 µM.[33] *Penicillium janthinellum* HDN13-309 produced trichodermamide B **[33]** which showed inhibition against cancer cells MGC803, HL-60, HO-8910, and K562 with IC_{50} values of 1.60, 1.80, 1.90, and 8.00 µM.[34] Meanwhile, phaeosphamide A **[34]** which was produced by *Phaeosphaeriopsis* sp. S296 isolated from *Bruguiera gymnorhiza* showed inhibition against AGS cells with an IC_{50} value of 5.14 µM.[35] The structures of the peptide group compounds are shown in **Figure 4**.

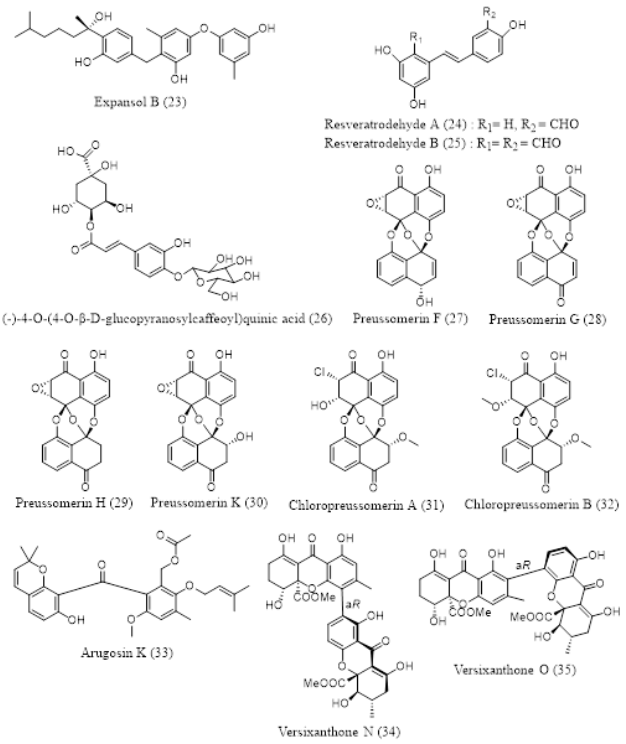

Figure 4. Chemical structures of peptides compounds from mangrove-derived fungi

Alkaloids

Alkaloids are a large group consisting of diverse subgroups of natural products that are most studied in plants. However, several studies have shown the presence, of alkaloids with promising medicinal properties in other types of organisms, such as fungi, especially in mangrove-derived fungi.[36] *Aspergillus* sp. FSY-01 and *Aspergillus* sp. FSW-02 is a fungal strain of the *Aspergillus* genus that was isolated from Rotten fruit of the mangrove *Avicennia marina* in Zhanjiang, Guangdong province, P. R. China, identified produces the same metabolite compound, namely neoaspergillic acid **[35]** which inhibits the growth of cancer cells K562 and SGC-7901 with IC_{50} value of 8.00 and 8.20 µM.[37]

Bionectria ochroleuca, isolated from inner leaf tissues of *Sonneratia caseolaris* in Hainan island, China, was identified to produce an alkaloid group, namely verticillin D **[36],** known to inhibit L5178Y cell with IC_{50} value of <0.10 µM (Ebrahim et al., 2012). Moreover, an alkaloid, called meleagrin **[37]**, was successfully isolated from the culture of *Penicillium* sp. GD6 residing in the stem bark of *Bruguiera gymnorrhiza*. This compound was found to inhibit the proliferation of A549 and HL60 cell lines with IC_{50} values of 8.3 and 9.70 µM, respectively.[38] A total of three metabolites of the chaetoglobosin group were produced from the *Penicillium chrysogenum* V11 strain associated with the *Myoporum bontioides* mangrove from the Guangdong Province, China. These compounds were assigned as cytoglobosin C **[38]**, which can inhibit A549 and SGC-7901 with IC_{50} value of 3.35 and 8.15 µM; chaetoglobosin A **[39]** which inhibited A549 and SGC-7901 cells with IC_{50} value of 6.56 and 7.48 µM; and penochalasin I **[40]** which inhibited SGC-7901 and MDA-MB-435 cells with IC_{50} value of 7.32 and 7.55 µM.[39]

The *Chaetomium globosum* kz-19 succeeded in producing five secondary metabolites with different cell inhibition, namely, chaetoglobocin C **[41]** was known to inhibit the growth of A549 cells with an IC_{50} value of 7.60 µM, chaetoglobocin V, E **[44, 42]** can inhibit HeLa cells with IC_{50} values of 3.80 and 7.50 µM. Meanwhile, chaetoglobosin G **[43]** could inhibit HeLa and A549 with IC_{50} values of 3.70 and 7.30 µM. Phychaetoglobin D **[45]** is known to inhibit HeLa cells with an IC_{50} value of 9.20 µM.[21] *Phomopsis asparagi* DHS-48 isolated from the fresh root of *Rhizophora mangle* is known to produce a secondary metabolite, phomoparagin D **[46]** which is known to show inhibition of HeLa cells with an IC_{50} value of 5.82 µM.[23] (**Figure 5**).

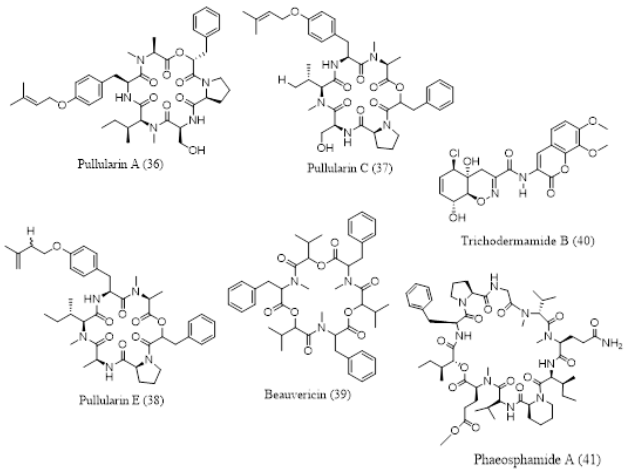

Figure 5. Chemical structures of cytotoxic alkaloids from mangrove-derived fungi

Among twelve alkaloids described in this review, ten of them bear indole moiety in their molecular structures. Many reports have shown compounds containing indole moiety revealed various bioactivities including anticancer, which suggested that indole part may play significant contribution to the bioactivity of the indole alkaloid type of compounds.

Pyrones

Compounds from the pyrone group, aspergisocoumrin A and B **[47-48]** were obtained from *Aspergillus* sp. HN15-5D isolated from leaves of

the mangrove plant *Acanthus ilicifolius* in Hainan Island, China. These metabolites were reported to inhibit MDA-MB-435 with IC_{50} values of 5.08 and 4.98 µM.[40] Configuration of the 1,3-diene at the side chain of the two compounds, where *trans* configuration found in **[47]** while *cis* configuration observed in **[48]** has no influence on the cytotoxic effect of these compounds, as both of them showed almost identical IC_{50} values against breast cancer cells MDA-MB-435.

Furthermore, *Fusarium* sp. 2ST2, a fungal strain of the *Fusarium* genus that was isolated from leaves of *Kandelia candel* in the South China Sea, Hainan Province, China, was revealed to produce 4H-1-benzopyran-4-one-2,3-dihydro-5-hydroxy-8-(hydroxylmethyl)-2-methyl **[49]** which inhibited MDA-MB-435 and A549 cells with IC_{50} value of 3.80 and 5.60 µM. This fungal strain also produced fusarisetin E and F **[50-51]**, which were reported to inhibit A549 cells with IC_{50} values of 8.70 and 4.30 µM, respectively.[41] Substitution of two H atoms to O atoms forming a dioxo bridge in the fourth ring as found in compound **[51]** could enhance its cytotoxicity against A549 cells by two folds. Further structure modification and or optimization will be promising for the development of this compound as anticancer.

Fluoranthene

Fluoranthene is a PAH compound that belongs to the class of organic compounds and consists of two to six aromatic rings. A secondary metabolite called daldinone I **[52]** recovered from *Annulohypoxylon* sp. of the fruits of *Rhizophora racemosa* collected in Cameroon showed a cytotoxic effect against Ramos cell lines with IC_{50} value of 6.60 µM.[42] (**Figure 6**). Mechanistic study revealed that compound **52** induced apoptosis through its ability to activate caspase-3.[42] Activation of cysteine-dependent aspartate-directed proteases (caspases) is known as important mediators that induces the programmed cell death which is known as apoptosis.

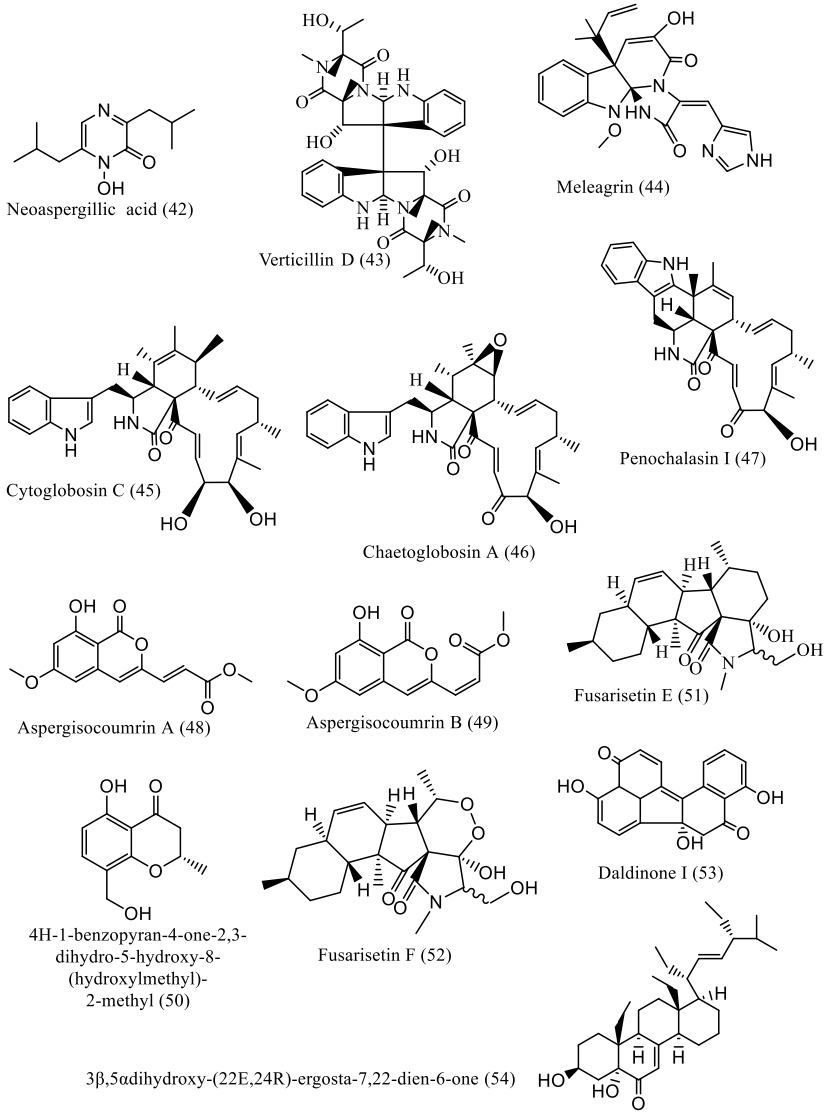

Figure 6. Chemical structures of cytotoxic pyrones, fluoranthene and terpenoid from mangrove-derived fungi

Terpenoid

Terpenoids have been reported to be the major component of essential oils for ages. They are derivatives of terpenes, which contain oxygen molecules. Some terpenoids exhibit an anticancer effect by triggering various stages of cancer progression, for example, suppressing the early stage of tumorigenesis via induction of cell cycle arrest, inhibiting cancer cell differentiation and activating apoptosis. Terpenoid compound 3β,5α-dihydroxy-(22E,24R)-ergosta-7,22-dien-6-one **[53]** was produced by *Aspergillus terreus* (No. GX7-3B) isolated from the branch of *Bruguiera gymnoihiza* (Linn.) Savigny. Based on in vitro tests against cancer cell types (HeLa, KB, A549, and MCF-7), compound **[53]** showed inhibition with IC_{50} values of 0.68, 1.50, 1.95, and 4.98 μM, respectively.[33] Other compound, asperterphenyllin G **[54]** isolated from the fungal strain *Aspergillus candidus* MK209104 associated with the root of *Rhizophora apiculata* Blume growing in Hainan Province, China, showed growth inhibition against a panel of cancer cells with IC_{50} values ranging from 0.40 to 6.00 μM.[16]

A growing number of anticancer metabolites have been discovered from mangrove-associated fungi. However, many of those compounds tend to show remarkable cytotoxicity not only towards cancer cells but also against normal cells, which challenge their further development in the discovery of anticancer agents. Therefore, cytotoxicity against both cancer and normal cells as the initial assay to screening potential cytotoxicity of natural products will be beneficial to show their selectivity against cancer cells, which can be used as consideration to decide further pharmacological investigation on the compounds under study.

CONCLUSION

A total of 54 secondary metabolites were found from 8 compound groups such as quinones, polyketides, phenols, peptides, alkaloids, pyrones, fluoranthene, and terpenoids. These secondary metabolites were produced by 16 genera of mangrove-derived fungi, some of which belong to the genus *Nigrospora*, *Cytospora*, *Aspergillus*, *Phaeosphaeriopsis*, *Alternaria*, and *Penicillium*. All of the compounds showed remarkable inhibitory activity towards cancer cells with IC_{50} values less than 10 μM. This finding puts mangrove-derived fungi as a promising source of future anticancer agents.

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CONFLICT OF INTEREST

We declare that we have no conflicts of interest to disclose regarding this article.

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