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REVIEW ARTICLE

Novel Anticancer Compounds from Endophytic Fungi

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Abstract: ***Background:*** The search for natural bioactive metabolites having potential anticancer property dates back to the *Ebers papyrus* written in 1550 BC. Natural products from medicinal plants and microorganisms are the most consistent and productive source for the "first-in-class" drugs. After two decades of research, a great deal of interest has been generated by discovery of remarkable pharmacological agents from endophytic fungi residing asymptomatically within plant tissues.

Objective: This review substantially covers the novel cytotoxic compounds isolated from endophytic fungi associated with terrestrial and mangrove plants as well as other microorganisms such as lichens, during 2011-2015. These natural compounds are described based on their cytotoxic activity profiles, chemical nature and potential structure–activity relationship deduced from the biochemical and cytotoxic studies. The anti-cancerous activities of the compounds discussed in this review are taken from the published reports exhibiting activity against specific cancer cell lines along with the mechanism of action. These compounds are exclusively isolated from endophytic fungi.

Conclusion: Endophytic fungi can be exploited for isolation of new reliable, economical and environmentally safe natural bioactive molecules having wide range of applications in agriculture, medicine and food industry. Over the past few decades much progress has been achieved though, still many issues such as optimizing the fermentation culture conditions for increasing the compound yield, elucidating biosynthetic pathway of the compounds in the endophytic fungi needs to be further clarified and resolved.

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Keywords: Anticancer, bioactive metabolites, endophytic fungi, medicinal plants, kinases.

1. INTRODUCTION

Fungi have long been known to possess the ability to produce bioactive secondary metabolites. Less than 16% of the fungal species described have been cultured and studied so far. Fewer than 5% of the total fungal species that have been characterized represent a vast source of natural bioactive metabolites [1]. Herein, we focus on fungal endophytes as they represent a wide source of unexplored and uncharacterized microorganisms capable of producing novel metabolites. Endophytes generally exist asymptomatically, coexisting with their hosts and represent underutilized group of microorganisms for discovery of new compounds. Endophytes are prolific producers of metabolites and have capability to produce compounds that are exclusively isolated from higher plants [2]. A recent literature survey indicated that 51% of the bioactive metabolites isolated from endophytic fungi were earlier unknown compared to 38% from soil fungi. This has led to a shift in current research towards finding a reliable, economical, environmentally safe and alternative method for isolation of bioactive compounds from these microorganisms.

Secondary metabolites from endophytic fungi have been recognized as potential source of anticancer compounds [3-6]. Various compounds including Camptothecin and several analogues [7-9], Vincristine and Podophyllotoxin [10,11], with anticancer activity have been isolated since the discovery of fungal derived Paclitaxel [2]. Moreover, development of resistance in cancer cell lines due to high rate of mutation compelled scientific community to search for novel anticancerous compounds. Thus, Endophytes could be exploited for isolation of bioactive secondary metabolites as they provide molecules with unique structure such as xanthones, tetralones, terpenoids, quinones, steroids, chinones, benzopyranones, alkaloids and phenolic acid having wide range of pharmaceutical applications.

In this review, we have attempted to cover recently reported novel metabolites having anticancer activity, discovered from endophytic fungi isolated from terrestrial plants, lichens and mangroves during 2011–2015. The compounds have been

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Table 1. Novel cytotoxic compounds reported from endophytic fungi.

Sr. no.	Compounds	Chemical nature	Cell line	IC_{50} value	Fungus	Source	Part	References
1.	Chaetoglobosin X (#1)	Polyketides	H22, MFC	3.125, 6.25 µg/mL	*Chaetomium globosum*L18	*Curcuma wenyujin*	Leaf	(12)
2.	Dothiorelone F (#2)	Polyketides	Raji	2 µg/mL	*Dothiorella* sp.	*Aegiceras corniculatum*	Bark	(13)
3.	Epicocconigrone A (#3)	Polyketides	RAJI	50% inhibition of proliferation by 72 h at 5 µM) and 30% cell death by 72 h, 25 µM)	*Epicoccum nigrum*	*Mentha suaveolens*	Leaf	(14)
4.	Periconiasin A (#4), Periconiasin B (#5)	Polyketides	HCT-8, BGC-823 HCT-8, Bel-7402, BGC-823	0.9, 2.1 µM 0.8, 5.1, 9.4 µM	*Periconia* sp. F-31	*Annona muricata*	Not Reported	(15)
5.	Chaetomugilide A (#6), Chaetomugilide B (#7), Chaetomugilide C (#8)	Nitrogen containing compounds (Alkaloid)	HepG-2 HepG-2 HepG-2	1.7 µM 19.8 µM 53.4 µM	*Chaetomium globosum* TY1	*Ginkgo biloba*	Bark	(16)
6.	Mycoleptodiscin B (#9)	Nitrogen containing compounds (Alkaloid)	H460, A2058, H522-T1, PC-3, IMR-90	0.660, 0.780, 0.630, 0.600, 0.41 µM	*Mycoleptodiscus* sp.	*Desmotes incomparabilis*	Leaf	(17)
7.	12-demethyl-12-oxo-eurotechinulin B (#10)	Nitrogen containing compounds	SMMC-7721	30 µg/mL	*Eurotium rubrum*	*Hibiscus tiliaceus*	Inner tissue	(18)
8.	PM181110 (#11)	Nitrogen containing compounds (Peptides)	40 human cancer cell lines 24 human tumorxenografts	0.089 µM 0.245 µM	*Phomopsis glabrae*	*Pongamia pinnata*	Leaf	(19)
9.	(-) - (4S,8S) -Foedanolide (#12) (+) - (4R,8R) -Foedanolide (#13)	Lactones	HeLa, A-549, U-251, HepG2 MCF-7 HeLa, A-549, U-251, HepG2, MCF-7	15.8, 296.0, 159.0, 22.8, 70.2 µg/mL 5.4 67.9 53.0 19.0 20.8 µg/mL	*Pestalotiopsis foedan*	*Bruguiera sexangula*	Branch	(20)
10.	Photipyrone B (#14)	Pyrones	MDA-MB-231	Inhibitory rate at 25.0% at 10 µg/mL	*Pestalotiopsis photiniae*	*Roystonea regia*	Not Reported	(21)
11.	Myrotheciumone A (# 15)	Lactones	HepG2, SMMC-7721, A549, MCF-7, QSG-7701 HL-7702	5.36, 6.56, 5.88, 7.56, 16.30, 20.69 µM	*Myrothecium roridum*	*Ajuga decumbens*	Stem	(22)

12.	Phomopsidone A (#16)	Lactones	MDA-MB-435	63 µM	*Phomopsis* sp. A123	*Kandelia candel*	Foliage	(23)
13.	3-epi-Waol A (#17)	Lactones	MCF-7, HCT116, H460	22.46, 6.20, 1.0 mM	*Libertella blepharis*	*Olyralati folia*	Leaf	(24)
14.	4,5-dihydroxy-3- (2-hydroxyethyl) -1-methoxy-8-methoxycarbonylxanthone (I) (#18), 1,8-dihydroxy-4- (2-hydroxyethyl) -3-methoxyxanthone (II) (#19)	Xanthones	NB4, A549, SHSY5Y, PC3, MCF7, NB4, A549, SHSY5Y, PC3, MCF7	5.2, 2.6, 6.3, 2.4 8.5 µM 5.9, >10, 4.8, >10, 8.2 µM	*Phomopsis amygdale*	*Paris axialis*	Rhizome	(25)
15.	1,5-dihydroxy-3-(2-oxopropyl)-6-methoxycarbonylxanthone (#20) 1-hydroxy-3-(2-oxopropyl)-8-methoxycarbonylxanthone (#21)	Xanthones	NB4, A549, SHSY5Y, PC3, MCF7 NB4, A549, SHSY5Y, PC3, MCF7	8.4, 3.6, >10, >10, 2.7 µM 6.5, 4.8, >10, >10, 5.1 µM	Phomopsis sp.	*Paris polyphylla* var. yunnanensis	rhizome	(26)
	3-O- (6-O-α-L-arabinopyranosyl) -β-D-glucopyranosyl-1,4 dimethoxyxanthone (#22)	Xanthone derivative	HEp-2, HepG2	9, 16 µmol/mL	*Phomopsis* sp.(ZH76)	*Excoecaria agallocha*	Stem	(27)
16.	Talaperoxide B (#23) Talaperoxide D (#24)	Peroxides	MCF-7, MDA-MB-435, HepG2, HeLa, PC-3 MCF-7, MDA-MB-435, HepG2, HeLa, PC-3	1.33, 2.78, 1.29, 1.73, 0.89 µg/mL 1.92, 0.91, 0.90, 1.31, 0.70 µg/mL	*Talaromyces flavus*	*Sonneratia apetala*	Leaf	(28)
17.	2,3-didehydro-19α-hydroxy-14-epicochlioquinone B (#25)	Quiinones	MCF-7, SW1990, SMMC7721	4, 5, 7 µg/mL	*Nigrospora* sp. MA75	*Pongamia pinnata*	Stem	(29)
18.	9-dehydroxyeurotinone (#26)	Quinones	SW1990	25 µg/mL	*Eurotium rubrum*	*Hibiscus tiliaceus*	Inner tissue	(18)
19.	Phomoarcherin A (#27) Phomoarcherin B (#28)	Terpenoids (Sesquiterpenes)	KKU-M213 KKU-100, KKU-M139, KKU-M156, KKU-M213, KKU-M214, KB KKU-100, KKU-M139, KKU-	16.6 µg/mL 8.0, 0.1, 2.0,	*Phomopsis archeri*	*Vanilla albidia*	Stem cortex	(30)

	Phomoarcherin C (#29)		M156, KKU-M213, KKU-M214	20, 5.0, 9.4 µg/mL 8.9, 8.9, 18.0, 15.4, 18.8 µg/mL				
20.	Geopyxin B (#30),	Terpenoids (Diterpenoids)	NCI-H460, SF-268 , MCF-7, PC-3M, MDA-MB-231	2.25, 2.35, 4.32 , 5.41, 3.31 µM	*Geopyxis aff. majalis*	*Pseudevernia intensa* (Lichen)	Thallus	(31)
21.	Cercosporene F (#31)	Terpenoids (Diterpenes)	HeLa, A549, MCF-7, HCT116, T24	19.3, 29.7, 46.1, 21.3, 8.16 µM	*Cercospora* sp.	*Fallopia japonica*	Leaf	(32)
22	Pestalol B (#32)	Others	MCF-7, BT474, A549, DU145, H1975, SK-BR-3, K562, MOLT-4, U937, BGC823 MCF-7, BT474, A549, DU145, H1975, SK-BR-3, K562, MOLT-4, U937, BGC823	42.5, >50, 40.2, 38.3, 27.7, 47.1, 36.2, 26.9, 25.1, 32.8 µM	*Pestalotiopsis* sp. AcBC2	*Aegiceras corniculatum*	Stem	(33)
	Pestalol C (#33)			>50, 39.1, >50, 38, 26.8 , >50, >50, 23.4, 29.7, >50 µM				
23.	Chloropestolide B (#34)	Others	A375, CNE1-LMP, MCF-7	9.9 16.4,	*Pestalotiopsis fici*	*Combretum leprosum*	Branch	(34)

				23.6 µM				
24.	Chloropupukeanolide C (#35) Chloropupukeanolide D (#36) Chloropupukeanolide E (#37)	Others	HeLa, HT29, L6 HeLa, HT29, L6 HeLa, HT29, L6	2.3, 1.2, 31.8 µM 7.9, 4.2 µM, inactive 61.50, 9.50, 12.3 µM	*Pestalotiopsis fici*	*Camellia sinensis*	Branches	(35)
25.	Pestaloquinol A (#38) Pestaloquinol B (#39)	Others	HeLa	8.8 µM for both	*Pestalotiopsis* sp.	*Podocarpus macrophyllus*	Branch	(36)
26.	Isochromophilone X (#40)	Others	MCF-7, SGC-7901, SW1116, A549, A375	14.90, 16.84, 24.15, 26.93, 35.75 µM	*Diaporthe* sp.	*Rhizophora stylosa*	Leaf	(37)
27.	Multirostratin A (#41) 20-oxo-deoxaphomin (42)	Others	HL-60, A-549, SMMC-7721, MCF-7, SW-480 HL-60, A-549, SMMC-7721, MCF-7, SW-480	7.8, 9.8, 10.8, 11.6, 15.8 µM 14.2, 10.4, 7.7, 9.6, 11.6 µM	*Phoma multirostrata* EA-12	*Eupatorium adenophorum*	Leaf	(38)
28.	Diaporine A (#43)	Others	HeLa, HepG2, A549, NCIH460, MCF-7	> 20 µM > 20 µM 4.514 µM 2.087 µM > 20 µM	*Diaporthe*sp.3lp-10	Not Reported	Not Reported	(39)
29.	Secoemestrin D (# 44),	Others	NCI-H460, SF-268, MCF-7, PC-3M, MDAMB-231, CHP-100, Wi-38	0.15, 0.06, 0.14, 0.17, 0.06, 0.10, 0.24 µM	*Emericella* sp. *AST0036*	*Astragalus lentiginosus*	Leaf	(40) (91)
30.	Cytospolide B (#45) Cytospolide E (#46)	Lactones	A-549 A-549	5.15 µg/mL 7.09 µg/mL	*Cytospora* sp. (strain No. ZW02)	*Ilex canariensi*	Not Reported	(41)
31.	3-epi-Steperoxide A (47)	Peroxide	MOLT-3, HuCCA-1, A549, HepG2, HL-60, MDA-MB-231, T47D, HeLa	0.68–3.71 µg/mL	*Pseudolagarobasidiumacaciicola*	*Bruguiera gymnorrhiza*	Not Reported	(42)
32.	Perenniporin A (#48)	Terpenoids (Sesquiterpenoid)	HeLa SMMC-7721	30.44, 45.49,	*Perenniporia tephropora* Z41	*Taxuschinensis var. mairei*	Bark	(43)

			PANC-1	44.22 µg/mL				
33.	Duclauxamide A1 (#49)	Polyketides	HL-60, SMML-7721, A-549, MCF-7, SW480	11−32 µM	*Penicillium manginii*YIM PH30375	*Panax notoginseng*	Root	(45)
34.	Penicitide A (#50)	Polyketides	HepG2	32 µg/mL	*Penicillium chrysogenum* QEN-24S,	*Laurencia* sp.	Inner tissue	(46)
35.	Acremoxanthone E (#51)	Polyketides	U251, PC-3, K562, HCT-15, MCF-7, SKLU-1	5.32, 8.62, ND, 10.27, 7.39, 1.16 µM	*Acremonium camptosporum*	*Bursera simaruba*	Leaf	(47)
36.	Aspergilline A (#52)	Nitrogen containing compounds (Alkaloid)	NB4, A549, SHSY5Y, PC3, MCF7	3.8, 1.2, 3.4, 2.6, 1.5 µM	*Aspergillus vesicolor*	*Paris polyphylla* var. yunnanensis	Rhizome	(48)
	Aspergilline B (#53)		NB4, A549, SHSY5Y, PC3, MCF7	7.2, >10, 5.4, 2.6, 4.5 µM				
	Aspergilline C (#54)			1.2, 2.8, 1.5, 2.8, 3.6 µM				
37.	Penicibrocazine A (#55)	Nitrogen containing compounds (Diketopiperazine)	Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990, SW480, U251	4.2, 6.8, 6.4, 5.5, 4.9, 2.6, 6.0, 2.0, 5.2 µM	*Penicillium brocae* MA-231	*Avicennia marina*	Fresh tissue	(49)
	Penicibrocazine B (#56)		Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990, SW480, U251 Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990,SW480, U251	3.6, 5.3, 5.5, 6.1, 4.0, 2.4, 6.4, 1.2, 3.5 µM				

	Penicibrocazine E (#57) Penicibrocazine F (#58)			11.2, 4.3, 5.6, 9.0, 12.4, 3.3, 2.1, ND, 6.1 µM 1.7, 6.9, 2.9, 3.0, 0.89, 8.0, 5.9, ND, 5.3 µM				
38.	Alterporriol K (#59) Alterporriol L (#60)	Quinones	MDA-MB-435, MCF-7, MDA-MB-435, MCF-7	26.97 µM, 29.11 µM 13.11, 20.04 µM	*Alternaria* sp. ZJ9-6B	*Aegiceras corniculatum*	Fruit	(50)
39.	2,14-dihydrox-7-drimen-12,11-olide (#61)	Sesquiterpenes	Hep-G2, MCF-7	61, 41.7 µg /mL	*Aspergillus glaucus*	*Ipomoea batatas*	Leaf	(51)
40.	5-butyl-6- (hydroxymethyl) -4-methoxy-2H-pyran-2-one (#62) 4-methoxy-6-methyl-5- (3-oxobutyl) -2H-pyran-2-one (#63)	Pyrans	HL60, K562 HL60, K562	2.2, 4.5 µM 0.9, 1.5 µM	*Alternaria phragmospora*	*Vinca rosea*	Leaf	(52)
41.	Nigerapyrone B (#64)	Pyrones	HepG2	62 µM	*Aspergillus niger* MA-132	*Avicennia marina*	Inner tissue	(53)
42.	Dichlorodiaportinol A (#65)	Isocoumarin	MCF-7 HepG2	17.8, 39.6 µg/mL	*Trichoderma* sp.	*Myoporum bontioides*	Root	(54)
43.	Dihydronaphthalenone (#66) 5- hydroxyl dihydrofusarubin A (#67) 5-hydroxy dihydrofusarubin B (#68)	Phenolic compounds	KB, MCF-7, NCI-H187, Vero KB, MCF-7, NCI-H187, Vero KB, MCF-7, NCI-H187, Vero	31.69, >50, 23.10, >50 21.25, 10.99, 12.14, >50	*Fusarium* sp. BCC14842	Bamboo	Leaf	(55)

				23.59, 23.43, 13.47, 28.26				
44.	KL4 (6-Methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene- 11-one-5,6,7,8-tetralene-7-acetamide) (#69)	Others	THP-1, OVCAR-5, MCF-7, A-549, CV-1	23, 70, 35, 43, 80 (% growth inhibition at 100 µg/ml)	*Aspergillus* sp.	*Gloriosa superb*	Seed	(56)
45.	Asperterone B (#70) Asperterone C (#71)	Others	SW1116 SW1116	57.5 µM 71.0 µM	*Aspergillus terreus*MHL-P22	*Malus halliana*	Leaf	(57)
46.	Compound 1 (#72) Compound 2 (#73) Compound 6 (#74)	Others	MDA-MB-435, HepG2, HCT-116 A549 MDA-MB-435, HepG2, HCT-116 A549 MDA-MB-435, HepG2, HCT-116 A549	34.25, 24.56, 33.72, 37.82 µM 31.32, 23.87, 29.19, 34.06 µM 24.62, 17.92, 11.09, 16.63 µM	*Penicillium 303#*	Unidentified Mangrove plant	Not Reported	(58)
47.	Ginsenocin (#75),	Others	MKN45, LOVO, A549, MDA-MB-435, HepG2, HL-60	1.91, 2.20, 5.03, 1.39, 2.34, 0.49 µg/mL	*Penicillium melinii* Yuan-25 and *Penicillium janthinellum*Yuan-27	*Panax ginseng*	Root	(59)
48.	Embellicine A (#76) Embellicine B (#77)	Others	K562 K562	3.473 (8h), 2.855 (24h), 1.282 (48), 1.202 (72 h) 0.917(8h), 0.323 (24h), 0.250 (48h), 0.210 µM (72h)	*Embellisia eureka*	*Cladanthus arabicus*	Stem	(60)
49.	Cladosporone A (#78),	Others	K562, A549, HL-60, Huh-7, MCF-7, H1975, U937, BGC823, Hela, MOLT-4	14.3, 15.7, 29.9, 40.6, 21.3, 10.5, 17.0, 10.1, 53.7, 14.6	*Cladosporium* sp.	*Kandelia candel*	Flower	(61)
50.	2, 4-dihydroxy-2', 6-diacetoxy-3'-methoxy-5'-methyl-diphenyl ether (#79)	Others	HL-60	2.24 µg/mL	*Verticillium* sp.	*Rehmannia glutinosa*	Root	(62)

listed based on their chemical nature and biosynthetic origin. Brief description of the cytotoxic activity of these compounds against selected cancer cell lines is given. Mode of action of the isolated anticancer compounds has been described wherever possible. Many of these compounds are listed in Table **1**.

2. COMPOUNDS FROM ASCOMYCETES

Ascomycetes are an important class of fungi where there is formation of ascospores. Some genera of this class are prolific producer of bioactive metabolites. A large number of novel anticancer metabolites belonging to various class of compounds have been discovered from endophytic fungi belonging to this class.

2.1. Polyketides

Chaetoglobosin X (#1 in Fig. **1**) isolated from the culture extracts of the endophytic fungus *Chaetomium globosum* L18 isolated from the leaves of *Curcuma wenyujin*, collected in Zhejiang Province, Wenzhou, China, exhibited activity against cancer cell lines H22 and MFC with IC_{50}values of 3.125 and 6.25 μg/Ml [12].

A new polyketide, named Dothiorelone F (#2 in Fig. **1**) has been isolated from endophytic fungus *Dothiorella* sp. Isolated from the bark of *Aegiceras corniculatu*, collected from the estuary of Jiulong River, Fujian Province of China. Dothiorelone F displayed significant inhibition of Raji cancer cell line with IC_{50} values 2 μg/mL [13].

Epicocconigrone A (#3 in Fig. **1**) was isolated from an endophytic fungus *Epicoccum nigrum* associated with leaves of *Mentha suaveolens*, growing in Morocco. Epicocconigrone A showed potent inhibition of at least 15 protein kinases with IC_{50} values ranging from 0.07 to 4.48 μM. Moreover, Epicocconigrone A inhibited histone deacetylase (HDAC) activities with IC_{50} values of 9.8 μM. Further, in cell viability and proliferation assay, the compound displayed mainly cytostatic effects in human lymphoma RAJI and U-937 cell lines. Epicocconigrone A inhibited 50% of the proliferation of RAJI cells at72 h of treatment by 5 μM and induced about 30% cell death from 72 h of treatment by 25 μM. This compound had no effect on U-937 cell viability, while it induced a growth inhibition of 32% from 5 μM after 72 h of treatment [14].

Two new Cytochalasans, Periconiasins A and B (#4, #5 in Fig. **1**) have been isolated from endophytic fungus *Periconia* sp. F-31 residing in *Annona muricata*, found in Hainan Province, China. Periconiasin A selectively inhibited HCT-8 and BGC-823 cell lines with IC_{50} values of 0.9 and 2.1 μM, respectively. Periconiasin B displayed selective inhibition of growth in HCT-8, Bel-7402, and BGC-823 cancer cell lines with IC_{50} values of 0.8, 5.1, and 9.4 μM, respectively [15].

2.2. Alkaloids and Nitrogen Containing Compounds

Novel natural Azaphilones alkaloids, Chaetomugilide A, B, C (#6, #7, #8 in Fig. **1**) were isolated from endophytic fungus *Chaetomium globosum* TY1 associated with bark of *Ginkgo biloba,* in Linyi, Shandong province, China. All of these three compounds showed significant cytotoxicity towards human hepatoblastoma, HepG-2 with IC_{50} values of 1.7, 19.8 and 53.4 μM respectively [16].

A novel alkaloid, Mycoleptodiscin B (#9 in Fig. **1**) was extracted from an endophytic fungus *Mycoleptodiscus* sp. obtained from leaves of *Desmotes incomparabilis*, collected in Coiba National Park, Veraguas, Panama. Mycoleptodiscin B when tested against H460, A2058, H522-T1, PC-3 and IMR-90 displayed IC_{50} values of 0.660, 0.780, 0.630, 0.600, 0.41 μM [17].

12-demethyl-12-oxo-eurotechinulin B (#10 in Fig. **1**), isolated from the *Eurotium rubrum*, an endophytic fungus that was isolated from the inner tissue of the semi mangrove plant *Hibiscus tiliaceus*, collected from Hainan Island, China. This compound exhibited cytotoxicity against SMMC-7721 cell line with IC_{50} value of 30 μg/mL [18].

A novel depsipeptide, PM181110 (#11 in Fig. **1**) was isolated from an endophytic fungus *Phomopsis glabrae* (PM0509732) residing in leaves of *Pongamia pinnata* (L.) Pierre, collected from Karnala Bird Sanctuary near Panvel in Raigad District, Maharashtra, India. The compound displayed mean IC_{50} value of 0.089 μM against 40 human cancer cell lines and ex vivo efficacy (mean IC_{50}= 0.245 μM) towards 24 human tumor xenografts [19].

2.3. Lactones

Two spiro-Ɣ-lactone enantiomers named (-)-(4S,8S)-Foedanolide (#12 in Fig. **1**) and (+) - (4R,8R)-Foedanolide (#13 in Figure1) were isolated for the first time from the endophytic fungus *Pestalotiopsisfoedan* residing in branch of *Bruguiera sexangula*, in Hainan, China. Both of these two compounds exhibited moderate activities towards HeLa, A-549, U-251, HepG2 and MCF-7 cancer cell lines with IC_{50} value of 15.8 296.0 159.0 22.8 70.2 μg/mL and 5.4 67.9 53.0 19.0 20.8 μg/mL, respectively [20].

A novel Ɣ Lactone, Photipyrone B (#14 in Fig. **1**) was isolated from *Pestalotiopsis photiniae*, an endophytic fungus isolated from *Roystonearegia*, collected from Jianfeng Mountain, Hainan Province, People's Republic of China. Photipyrone B displayed inhibitory rate at 25.0% against MDA-MB-231 respectively at 10 μg/mL [21].

A novel bicyclic lactone, Myrotheciumone A (#15 in Fig. **1**) was isolated from endophytic fungus *Myrothecium roridum.* The fungus was isolated from stem of medicinal herb plant *Ajuga decumbens.* Myrotheciumone A exhibited potent cytotoxicity against HepG2, SMMC-7721, A549, MCF-7, QSG-7701 and HL-7702 cell Lines with IC_{50} values of 5.36, 6.56, 5.88,7.56, 16.30 and 20.69 μM respectively. Moreover this compound induced release of cytochrome c in HepG2 cells suggesting that this compound dramatically induced cytochrome c release in HepG2 cells and can induce apoptosis in HepG2 cells [22].

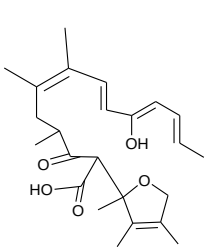
Phomopsidone A (#16 in Fig. **1**) was extracted from the *Phomopsis* sp. A123, an endophytic fungi obtained from the foliage of the mangrove plant, *Kandelia candel* (L.) Druce, collected from the mangrove nature conservation area of Fugong, Fujian, China. Phomopsidone A displayed an IC_{50} of 63 μM against MDA-MB-435 cell line [23].

3-epi-WaolA (#17 in Fig. **1**) was isolated from an endophytic fungus *Libertellable pharis* from mature leaves

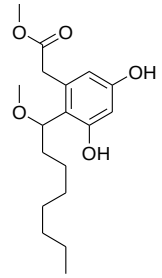
of *Oryza latifolia*, collected in the province of Colon, Republic of Panama. 3-epi-Waol A, showed cytotoxicity against MCF-7, HCT116, and H460 cancer cell lines with IC_{50} values of 22.46, 6.20, and 1.0 mM respectively [24].

2.4. Xanthones

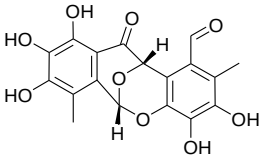
Phomopsis, another important genus exists as an endophyte in most plants and is also extremely



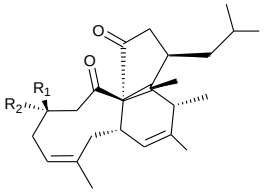
Chaetoglobosin X (#1)



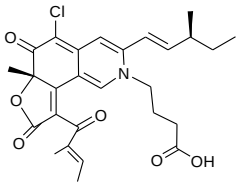
Dothiorelone F (#2)



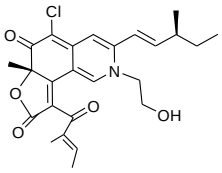
Epicocconigrones A (#3)



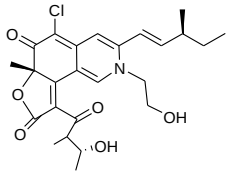
R_1 = H, R_2 = OH, Periconiasin A (#4)
R_1 = OH, R_2 = H, Periconiasin B (#5)



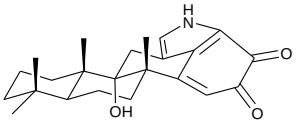
Chaetomugilide A (#6)



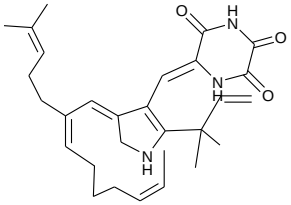
Chaetomugilide B (#7)



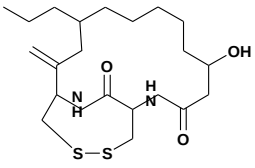
Chaetomugilide C (#8)



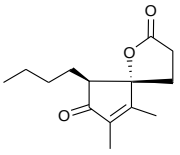
Mycoleptodiscin B (#9)



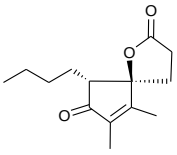
12-demethyl-12-oxo-eurotechinulin B (#10)



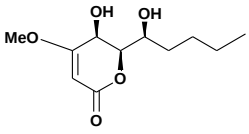
PM 181110 (#11)



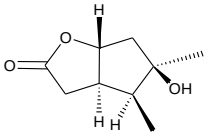
(-)-(4S,8S)-Foedanolide (#12)



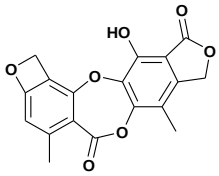
(+)-(4R,8R)-Foedanolide (#13)



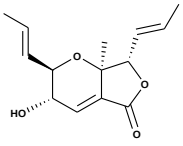
Photipyrone B (#14)



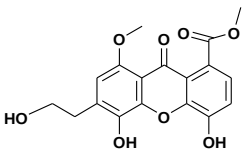
Myrotheciumone A (#15)



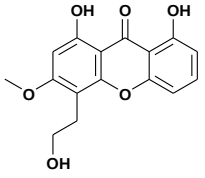
Phomopsidone A (#16)



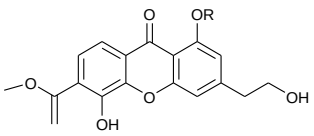
3-epi-Waol A (#17)



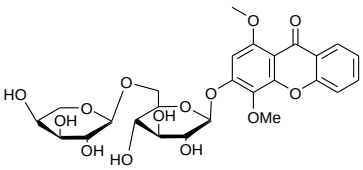
4,5-dihydroxy-3-(2-hydroxyethyl)-1 -methoxy-8-methoxycarbonyl xanthone (#18)



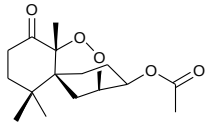
1,8-dihydroxy-4- (2-hydroxyethyl) -3-methoxyxanthone (#19)



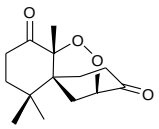
R = H, 1,5-dihydroxy-3-(2-oxopropyl)-6-methoxycarbonyl (#20)
R = Me, 1-hydroxy-3-(2-oxopropyl)-8-methoxycarbonylxanthone (#21)



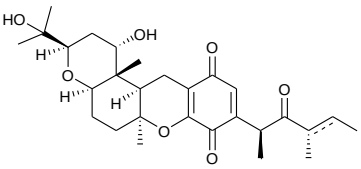
3-O-(6-O-a-L-arabinopyranosyl)-b-D-glucopyranosyl-1,4 dimethoxyxanthone (#22)



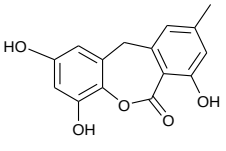
Talaperoxides B (#23)



Talaperoxides D (#24)



2,3-didehydro-19?-hydroxy-14-epicochlioquinone B (#25)



9-dehydroxyeurotinone (#26)

Fig. (1). Structures of novel anticancer metabolites isolated from Ascomycetes (#1-#26).

biochemically diverse. Cytotoxic compounds 4,5-dihydroxy-3- (2-hydroxyethyl)-1-methoxy-8-methoxycarbonylxanthone) and 1,8-dihydroxy-4-(2-hydroxyethyl)-3-methoxyxanthone (#18, #19 in Fig. **1**) were isolated from *Phomopsis* species from the rhizomes of *Paris axialis* collected from Heqing County, Dali prefecture, Yunnan Province, People's Republic of China. The two compounds were tested against NB4, A549, SHSY5Y, PC3, MCF7 cell lines. The former compound showed moderate cytotoxicity with IC_{50} values of 5.2, 2.6, 6.3,2.4 and 8.5 μM while latter compound showed IC_{50} values of 5.9, >10, 4.8,, >10, 8.2 μM, respectively towards tested cell lines The reference compound, Taxol showed cytotoxicity against NB4, A549, SHSY5Y, PC3, MCF7 cells with IC_{50} values of 0.03, 0.02, 0.2, 0.2 and 0.1 μM, respectively [25].

Two new xanthones, 1,5-dihydroxy-3-(2-oxopropyl)-6-methoxycarbonylxanthone and 1-hydroxy-3-(2-oxopropyl)-8-methoxycarbonylxanthone (#20, #21 in Fig. **1**) were extracted from the endophytic fungus *Phomopsis* sp. isolated from rhizome of *Paris polyphylla* var. yunnanensis collected from ShiZhong, Yunnan, People's Republic of China. Both of these compounds showed cytotoxicity against NB4, A549, SHSY5Y, PC3, MCF7 cell lines with IC_{50} values of 8.4, 3.6, >10, >10 and 2.7 μM and 6.5, 4.8, >10, >10 and 5.1 μM, respectively, while Paclitaxel exhibited cytotoxicity against NB4, A549, SHSY5Y, PC3, MCF7, cell lines with IC_{50} values of 0.03 0.02 0.2 0.2 and 0.1 μM respectively [26].

Xanthone-O-glycoside,3-O-(6-O-α-L-arabinopyranosyl)-β-D-glucopyranosyl-1,4dimethoxy xanthone (#22 in Fig. **1**) was isolated from endophytic fungus *Phomopsis* sp. (ZH76) isolated from stem of *Excoecaria agallocha* of the mangrove tree Euphorbiaceae from Dong Sai of the South China Sea coast. This compound exhibited cytotoxicity against HEp-2 and HepG2 cells with, IC_{50} values of 9 and 16 μmol/mL respectively [27].

2.5. Peroxides

Talaperoxides B and D (#23 and #24 in Fig. **1**) were isolated from *Talaromyces flavus* residing in leaves of a mangrove plant *Sonneratia apetala*, from Dongzhaigang Mangrove National Nature Reserve in Hainan Island, China. Talaperoxides B and D showed cytotoxicity against MCF-7, MDA-MB-435, HepG2, HeLa, and PC-3 with IC_{50} values 1.33 2.78 1.29 1.73 0.89 and 1.92 0.91 0.90 1.31 0.70 μg/mL respectively [28].

2.6. Quinones

A novel cytotoxic compound 2,3-didehydro-19α-hydroxy-14-epicochlioquinone B (#25 in Fig. **1**) was isolated from *Nigrospora* sp. MA75 residing in stem of marine mangrove plant *Pongamia pinnata*, which was collected from Guangxi Zhuang an autonomous region of China. The isolated compound displayed cytotoxic activity against MCF-7, SW1990, and SMMC7721 cell lines with IC_{50} value of 4, 5, and 7 μg/mL, respectively [29].

9-dehydroxyeurotinone (#26 in Fig. **1**) isolated from the *Eurotium rubrum*, an endophytic fungus that was isolated from the inner tissue of the semi mangrove plant *Hibiscus tiliaceus*, collected from Hainan Island, China. 9-dehydroxyeurotinone displayed IC_{50} value of 25 μg/mL against SW1990 cell line [18].

2.7. Terpenoids

Three novel sesquiterpenes, Phomoarcherins A-C (#27, #28, #29 in Fig. **2**) were obtained from the *Phomopsis archeri* endophyte residing inside the stem of *Vanilla albidia*. Phomoarcherin B exhibited in vitro cytotoxic activity against KKU-100, KKU-M139, KKU-M156, KKU-M213, KKU-M214, and KB cell lines with IC_{50} values of 8.0, 0.1, 2.0, 20, 5.0 and 9.4 μg/mL, respectively. Phomoarcherin C exhibited in vitro cytotoxic activity against KKU-100, KKU-M139, KKU-M156, KKU-M213, and KKU-M214 cell lines with IC_{50} values 8.9, 8.9, 18.0, 15.4, and 18.8 μg/mL, respectively. Phomoarcherin A exhibited in vitro cytotoxic activity against KKU-M213 cell lines with IC_{50} values of 16.6 [30].

A novel ent-kauranediterpenoids Geopyxin B (#30 in Fig. **2**) was isolated from *Geopyxis* aff. *Majalis.* Geopyxin B exhibited cytotoxicity against NCI-H460, SF-268, MCF-7, PC-3M and MDA-MB-231 cell lines with IC_{50} values of 2.25, 2.35, 4.32,5.41 and 3.31 μM respectively [31].

A new Guanacastane diterpene, Cercosporene F (#31 in Fig. **2**) from an endophytic fungus *Cercospora* sp. isolated from leaves of *Fallopia japonica*, collected at Mingyue Mountain, Jiangxi Province, People's Republic of China. Cercosporene F exhibited potent cytotoxicity against five human tumor cell lines, HeLa, A549, MCF-7, HCT116 and T24 with IC_{50} values of 19.3, 29.7, 46.1, 21.3, and 8.16 μM, respectively [32].

2.8. Others

The genus *Pestalotiopsis* exists as an endophyte in most of the world's rainforests and is extremely biochemically diverse. Some the compounds isolated from this group includes Pestalols B and C (#32 and #33 in Fig. **2**) extracted from the endophytic fungus *Pestalotiopsis* sp. AcBc2from the stem cuttings of *Aegiceras corniculatum.* Pestalols B and C showed cytotoxicity against a panel of 10 tumor cell lines MCF-7, BT474, A549, DU145, H1975, SK-BR-3, K562, MOLT-4, U937, BGC823 with IC_{50} value of 42.5, >50, 40.2, 38.3, 27.7, 47.1, 36.2, 26.9, 25.1, 32.8μM and >50, 39.1, >50, 38.0, 26.8, >50, >50, 23.4, 29.7, >50 μM respectively [33].

A new metabolite, Chloropestolides B (#34 in Fig. **2**) featuring the chlorinated spiro[benzo[d][1,3]dioxine-2,7'-bicyclo[2.2.2]octane]-4,8'-dione was obtained from endophytic fungus *Pestalotiopsis fici* isolated from branches of plant *Combretum leprosum*, found in suburb of Hangzhou, People's Republic of China. Chloropestolides B showed cytotoxicity to, A375, CNE1-LMP1 and MCF-7 with IC_{50} values of 9.9, 16.4 and 23.6 μM, respectively [34].

Three natural bioactive compounds Chloropupukeanolides C-E, (#35-#37 in Fig. **2**) exhibiting a novel spiroketal skeleton were also isolated from endophytic fungus *Pestalotiopsis fici* growing in branches of plant *Camellia sinensis*, a suburb of Hangzhou, People's Republic of China. Chloropupukeanolides C-E showed significant cytotoxicity against HeLa (2.3, 1.2 μM), HT29 (7.9, 4.2 μM)

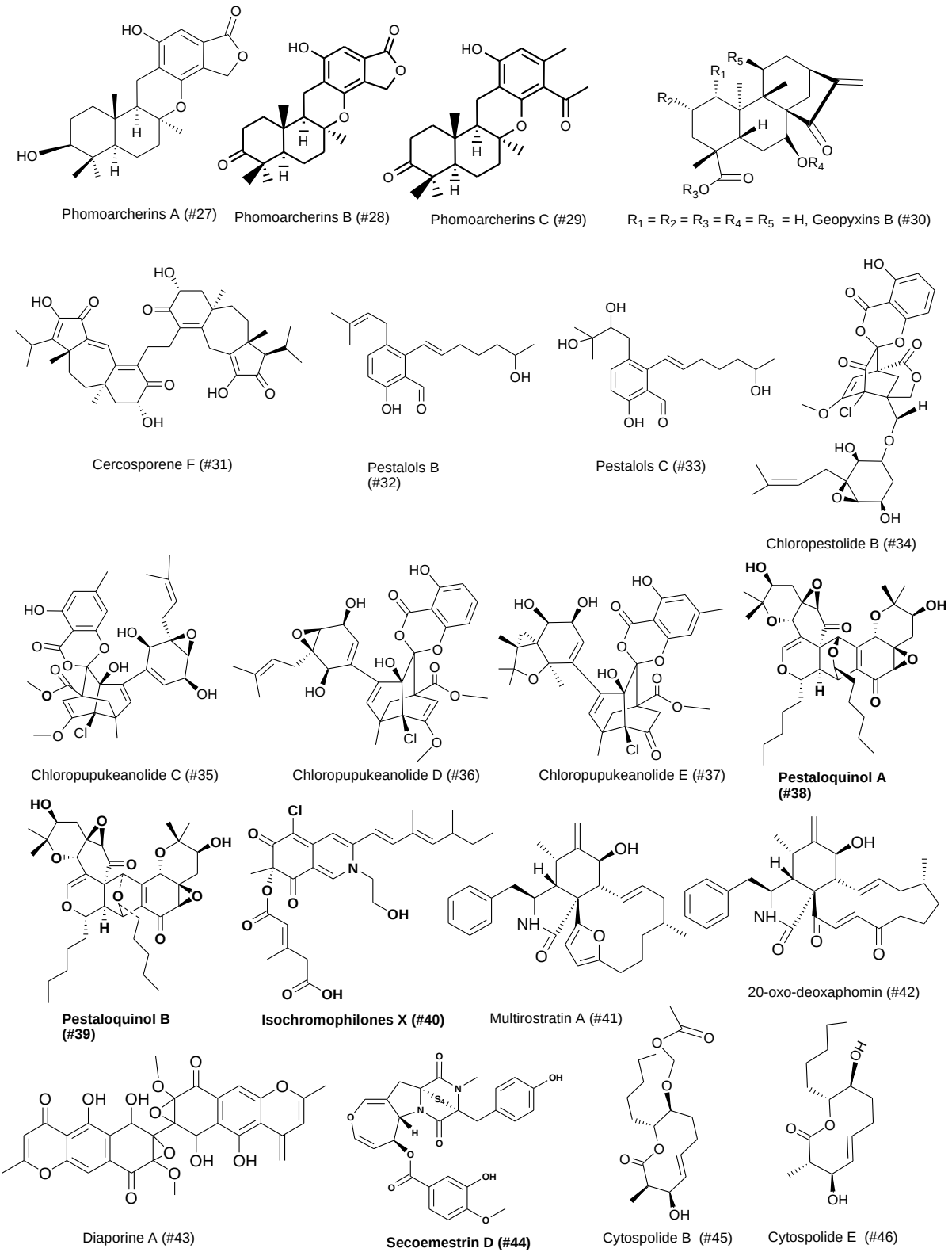


Fig. (2). Structures of novel anticancer metabolites isolated from Ascomycetes (#27-#44) and Basidiomycetes (#45-46).

and L6 cell (61.50, 9.50, 12.3 µM). Compound #37 was inactive against HT29 cell line and displayed weak cytotoxic effect against HeLa with IC_{50} value of 31.8 µM [35].

Chemical investigation of *Pestalotiopsis* sp. isolated from branch of *Podocarpus macrophyllus*, collected from D. Don at Kunming World Horticultural Exposition Garden, Kunming, People's Republic of China yielded two novel isoprenylated epoxyquinol derivatives, Pestaloquinols A and B (#38 and #39 in Fig. **2**). Both compounds displayed cytotoxicity against HeLa cells with same IC_{50} value of 8.8 µM [36].

Isochromophilone X (#40 in Fig. **2**), a cytotoxic compound isolated from endophytic fungus *Diaporthe* sp. residing in leaves of *Rhizophora stylosa* from the mangrove forest of Hainan Province of China. This compound showed moderate cytotoxic activities with its IC_{50} values of 14.90, 16.84, 24.15, 26.93 and 35.75 μM against MCF-7, SGC-7901, SW1116, A549 and A375 cell lines respectively [37].

Diaporthe is another genus which Produce diverse compounds. Here are some examples of bio-active compounds produced by this fungus. Two novel cytochalasins named Multirostratin A and 20-oxo-deoxaphomin (#41 and #42 in Fig. **2**) from *Phoma multirostrata* EA-12, an endophytic fungus found in the leaves of *Eupatorium adenophorum* collected in Kunming Institute of Botany, Kunming, Yunnan province, PR China. Multirostratin A and 20-oxo-deoxaphomin exhibited cytotoxic activity against HL-60, A-549, SMMC-7721, MCF-7 and SW-480 cell lines with IC_{50} values of 7.8, 9.8, 10.8, 11.6, 15.8 μM and 14.2, 10.4, 7.7, 9.6 and 11.6 μM respectively. The positive control Cisplatin showed the cytotoxic activity against HL-60, A-549, SMMC-7721, MCF-7 and SW-480 cell lines with IC_{50} values of 1.0, 4.3, 5.1, 15.4 and 15.4 μM respectively [38].

Diaporine A (**#**43 in Fig. **2**), a novel small-molecule compound from endophytic fungus *Diaporthe* sp. 3lp-10 was shown to display potential anti-cancer activities. The compound was tested for toxicity against HeLa, HepG2, A549, NCIH460, and MCF-7 cancer cell lines. The cells were treated with Diaporine A (0.625~20 μM) for 48 h and their viabilities were tested using the CCK-8 assay. The compound showed different cytotoxicity on different cells. Among these five tested cell lines, NCI-H460 (IC_{50} values, 2.087 μM) and A549 (IC_{50} values, 4.514 μM) exhibited more sensitivity to Diaporine A than other cells (IC_{50} values, > 20 μM). This new compound efficiently inhibited the viability, proliferation, and colony forming of NSCLC cell lines in concentration- and time-dependent manner. It caused cell cycle arrest at the G1 phase and down regulated the expression of CCND1, CCNE1, CDK4, and CDK2. Moreover, it also suppressed the growth of cancer in vivo. Interestingly, Diaporine A up-regulated the expression of miR-99a, which was down regulated in various human lung cancer cells/tissues. Furthermore, miR-99a/mTOR pathway was involved in Diaporine A induced cell cycle arrest [39].

Investigation of endophytic fungus *Emericella* sp. AST0036 associated with leaves of *Astragalus lentiginosus,* collected from an open, disturbed area in the Verde Valley of central Arizona, afforded a new compound, Secoemestrin D (#44 in Fig. **2**). The compound exhibited cytotoxic activity against seven human cancer cell lines viz. NCI-H460, SF-268, MCF-7, PC-3M, MDAMB-231, CHP-100, Wi-38 with the IC_{50} value of 0.15, 0.06, 0.14, 0.17, 0.06, 0.10, and 0.24 μM respectively [40].

3. COMPOUNDS FROM BASIDIOMYCETES

3.1. Lactones

Cytospolide B and Cytospolide E (#45 and #46 in Fig. **2**) displaying strong cytotoxic activity against A-549 with IC_{50} values of 5.15 and 7.09 μg/mL, have been isolated from *Cytospora* sp., strain no. ZW02, an endophytic fungus residing in *Ilex canariensis,* collected from Gomera [41].

3.2. Peroxides

3-Epi-steperoxide A (#47 Fig. **3**) were extracted from *Pseudolagarobasidiumac aciicola,* an endophyte from *Bruguiera gymnorrhiza*. 3-Epi-Steperoxide A displayed potent cytotoxic activity against MOLT-3, HuCCA-1, A549, HepG2, HL-60, MDA-MB-231, T47D and HeLa cancer cell lines with IC_{50} ranges of 0.68–3.71μg/mL, respectively [42].

3.3. Terpenoids

Perenniporin A (#48 in Fig. **3**) was isolated from *Perenniporia tephropora* Z41, an endophytic fungus residing in bark of *Taxus chinensis* var. mairei, collected in Jingning, Zhejiang Province, PR China. Perenniporin A showed moderate cytotoxicity towards HeLa SMMC-7721 PANC-1 cell line with IC_{50} values of 30.44 45.49 44.22 μg/mL respectively [43].

4. COMPOUNDS FROM HYPHOMYCETES

Hyphomycete form a class of fungi which produces the asexual spores *Aspergillus*, *Penicillium, Fusarium* and *Alternaria* are well known endopytic fungi and are known to produce diverse metabolites.

4.1. Polyketides

Penicillum is an important genus since the discovery of Penicillin (44) and is also known to produce cytotoxic compounds. Duclauxamide A1 (#49 in Fig. **3**), from the fungal endophyte *Penicillium manginii* residing in roots of plant *Panax notoginseng*, collected from Wenshan region of Yunnan province, Southwest China. The isolated compound displayed moderate cytotoxicity against HL-60, SMML-7721, A-549, MCF-7, and SW480 cancer cell lines with IC_{50} values in the range of 11−32 μM [45].

A cytotoxic compound Penicitide A (#50 in Fig. **3**) was isolated from *Penicillium chrysogenum* QEN-24S, an endophytic fungus isolated from marine red algae belonging to genus *Laurencia,* found growing in Weizhou Island of southern China Sea. Penicitides A exhibited moderate cytotoxic activity towards HepG2 cell line with IC_{50} of 32 μg/mL [46].

A novel hetero dimeric polyketide, Acremoxanthone E (#51 in Fig. **3**), was extracted from the endophytic fungus *Acremonium camptosporum* obtained from the leaves of *Bursera simaruba* collected from the semideciduous dry tropical forest of the Ecological Reserve El Eden in the state of Quintana Roo, Mexico. Acremoxanthone E exhibited cytotoxicity against human cancer cell lines U251, PC-3, K562, HCT-15, MCF-7 and SKLU-1 with IC_{50} values of 5.32, 8.62, ND, 10.27, 7.39, 1.16 μM [47].

4.2. Alkaloids and Nitrogen Containing Compounds

Aspergillines A−C (#52 - #54 in Fig. **3**) are highly oxygenated cyclopiazonic acid (CPA) -derived alkaloids bearing a rigid and sterically congested

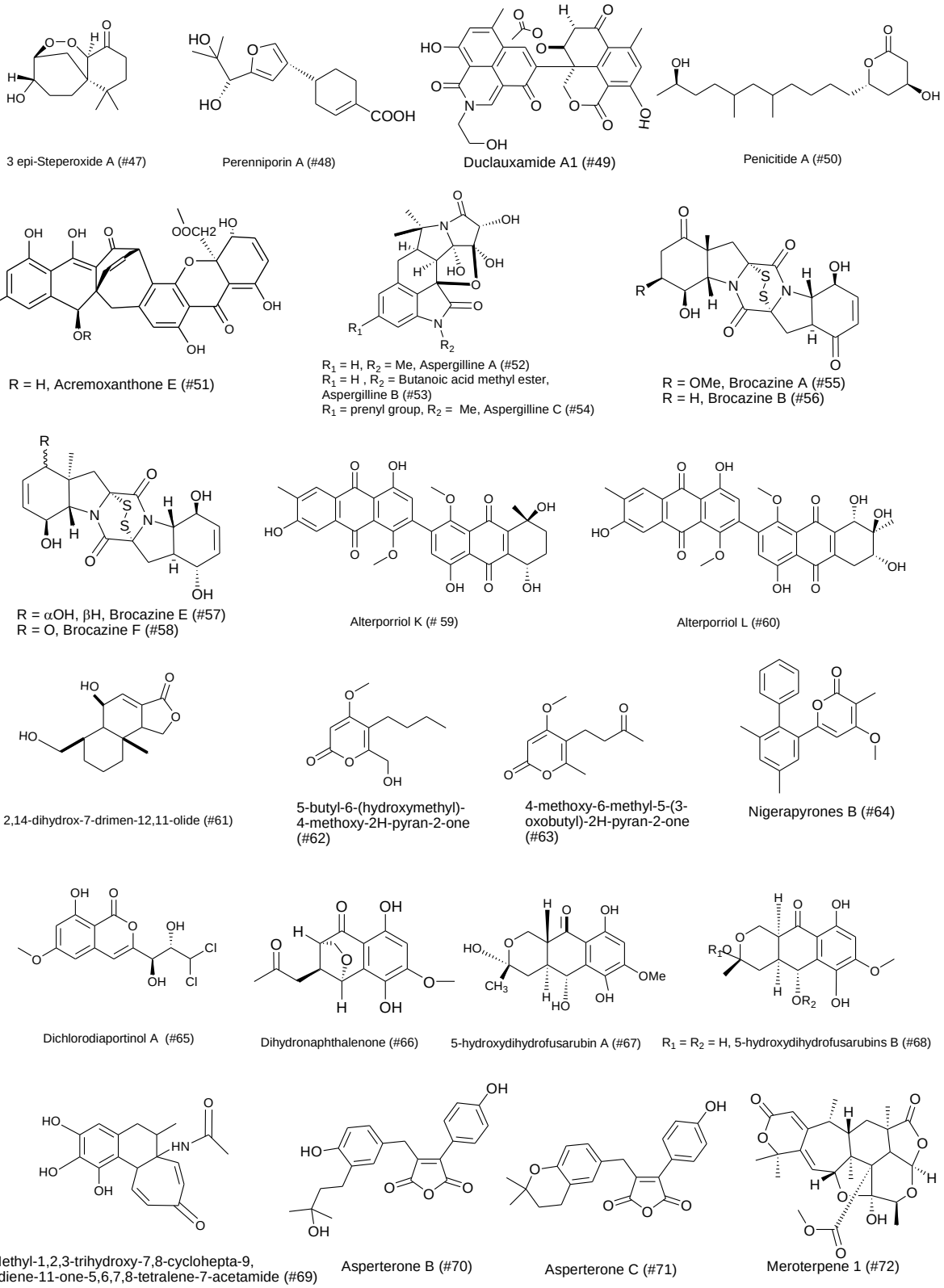


Fig. (3). Structures of novel anticancer metabolites isolated from Basidiomycetes (#47-#48) and Hyphomycetes (#49-#72).

~~hexacyclicindole~~–tetrahydrofuran– tetramate scaffold, isolated from the endophytic fungus *Aspergillus vesicolor* an endophyte isolated from Rhizome of *Paris polyphylla*. All these compounds were tested for cytotoxic activity against NB4, A549, SHSY5Y, PC3 and MCF7cell lines. All the three exhibited moderate cytotoxicity in all cell lines, with IC_{50} values of 3.8, 1.2, 3.4, 2.6, 1.5 μM (Aspergilline A), 7.2, >10, 5.4, 2.6, 4.5 μM (Aspergilline B) and 1.2, 2.8, 1.5, 2.8, 3.6 μM (Aspergilline C), respectively [48].

Four new disulfide-bridged diketopiperazine derivatives namely Penicibrocazine A B, E and F (#55- #58 in Fig. **3**)

were isolated from the endophytic fungus, *Penicillium brocae* MA- 231 from fresh tissue of *Avicennia marina*, collected at Hainan Island, P. R. China. All the four compounds exhibited cytotoxicity against Du145, HeLa, HepG2, MCF-7, NCI-H460, SGC-7901, SW1990, SW480, U251 cell lines with IC_{50} value in the range of 0.89-12.4 μM [49].

4.3. Quinones

Cytotoxic Alterporriol K and L (#59 and #60 in Fig. **3**) were isolated from endophyte *Alternaria*sp. ZJ9-6B isolated from fruit of *Aegiceras corniculatum* collected in Zhanjiang Mangrove, Guangdong province, P.R. China. Alterporriol K had an IC_{50} value of 26.97 μM against MDA-MB-435 and 29.11 μM against MCF-7 cells, respectively. Alterporriol L showed activities against MDA-MB-435 (IC_{50} = 13.11 μM) and MCF-7 (IC_{50} = 20.04 μM) [50].

4.4. Terpenoids

A new Sesquiterpene 2,14-dihydrox-7-drimen-12,11-olide (#61 in Fig. **3**) has been isolated from endophytic fungus *Aspergillus glaucus* residing in leaves of *Ipomoea batatase*, obtained from the herbarium of Agriculture Research Center (ARC), Cairo. This compound exhibited cytotoxicity against Hep-G2 and MCF-7 cell lines with IC_{50} value 61 μg/mL and 41.7 μg /mL respectively [51].

4.5. Pyrans

Two novel pyrans, 5-butyl-6-(hydroxymethyl)-4-methoxy-2H-pyran-2-one and 4-methoxy-6-methyl-5- (3-oxobutyl) -2H-pyran-2-one (#62 and #63 in Fig. **3**) displayed moderate antileukemic activities against HL60 cells (IC_{50} values of 2.2 and 0.9 μM) and K562 cells (IC_{50} values of 4.5 and 1.5 μM). The compounds were obtained from *Alternaria phragmospora*, an endophytic fungus from *Vinca rosea* leaves [52].

4.6. Pyrones

α-Pyrone derivatives, Nigerapyrone B (#64 in Fig. **3**) were isolated from an endophytic fungus *Aspergillus niger* MA-132 isolated from inner tissue of marine mangrove plant *Avicennia marina*, collected at Dongzhai Harbor in Hainan, P. R. China. Nigerapyrone B showed selective activity against the HepG2 cell line with an IC_{50} of 62 μM. The positive control, fluorouracil showed cytotoxicity against tumor cell lines of A549, HepG2, DU145, MCF-7, SW1990, NCI-H460, and MDA-MB-231, with IC_{50} values of 52, 109, 3.3, 31, 121, 8.5, and 59 μM, respectively [53].

4.7. Coumarins

A new chlorine-containing isocoumarin, Dichlorodiaportinol A (#65 in Fig. **3**) was isolated from an endophytic fungus *Trichoderma* sp. residing in roots of *Myoporum bontioides*, collected in Leizhou Peninsula, Guangdong Province, China. This compound inhibited MCF-7 and HepG2 cell lines, with IC_{50} values of 17.8 and 39.6 μg/mL respectively [54].

4.8. Phenolic Compounds

Dihydronaphthalenone, 5-hydroxydihydrofusarubins A, B (#66, #67, #68, in Fig. **3**) were isolated from the endophyte *Fusarium* sp. BCC14842 of Bamboo leaf, collected from the Bamboo forest at Nam Nao National Park, Phetchabun Province, Thailand. The isolated Compounds displayed cytotoxicity against KB. MCF-7, NCI-H187 and Vero cells lines with IC_{50} value of 31.69 >50 23.10 >50 μg/mL (Dihydronaphthalenone), 21.25 10.99 12.14 >50 μg/mL (5-hydroxydihydrofusarubins A) and 23.59 23.43 13.47 28.26 μg/mL (5-hydroxydihydrofusarubins A) [55].

4.9. Others

A novel cytotoxic compound 6-Methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide (KL4) (#69 in Fig. **3**) was isolated from *Aspergillus* sp., an endophyte residing in seeds of medicinal plant *Gloriosa superb.* The compound significantly inhibited growth ofTHP-1, OVCAR-5, MCF-7, A-549 and CV-1 cell lines in a dose dependent manner with significant activity against THP-1 and MCF-7 cell line with IC_{50} value of 30 μg/mL and 50 μg/mL [56].

Two new Furandiones, Asperterone B and C (#70 and #71 in Fig. **3**) were isolated from an endophytic fungus*Aspergillus terreus* MHL-P22 associated with leaves of *Malus halliana* collected from the suburb of Nanjing, China. Asperterone B and C, displayed moderate antitumor effect with IC_{50} values of 57.5 and 71.0 μM respectively against human colorectal carcinoma SW1116 cells [57].

Two meroterpenes, Compound 1-2 (#72 in Fig. **3**, #73 in Fig. **4**) and one azaphilone, compound 6, (#74 in Fig. **4**) were isolated from an endophytic fungus *Penicillium 303#* from sea water collected from Zhanjiang Mangrove National Nature Reserve in Guangdong Province, China. These compounds showed cytotoxicity against MDA-MB-435, HepG2, HCT-116 and A549 cell lines with IC_{50} values of Compound #72 (34.25, 24.56, 33.72, 37.82 μM), Compound #73 (31.32, 23.87, 29.19, 34.06 μM), compound #74 (24.62, 17.92, 11.09, 16.63 μM) [58].

Ginsenocin (#75 in Fig. **4**) have been isolated from the endophytic fungus *Penicillium melinii* Yuan-25 and *Penicillium janthinellum* Yuan-27 from the roots of *Panax ginseng*, collected in Changchun, Jilin Province, People's Republic of China. Ginsenocin showed potent cytotoxic activity with IC_{50}values of 1.91, 2.20, 5.03, 1.39, 2.34, 0.49 μg/mL against six human cancer cell lines MKN45, LOVO, A549, MDA-MB-435, HepG2, and HL-60 [59].

Embellicines A and B (#76 and #77 in Fig. **4**) were isolated from *Embellisia eureka*, an endophytic fungus found in *Cladanthus arabicus*, collected in Morocco. Compounds (#76 and #77) inhibited NF-κB transcriptional activity with IC_{50} of 3.038 and 0.352 μM respectively. Further, in a cell viability assay, Embellicine A displayed IC_{50} values of 3.473 (8h), 2.855 (24h), 1.282 (48), and 1.202 (72 h) whereas Embellicine B showed IC_{50} value of 0.917 (8h), 0.323 (24h), 0.250 (48h) and 0.210 μM (72h), respectively against K562 cell line [60].

Cladosporone A (#78 in Fig. **4**) were isolated from an endophytic fungus isolated from *Cladosporium* sp. obtained

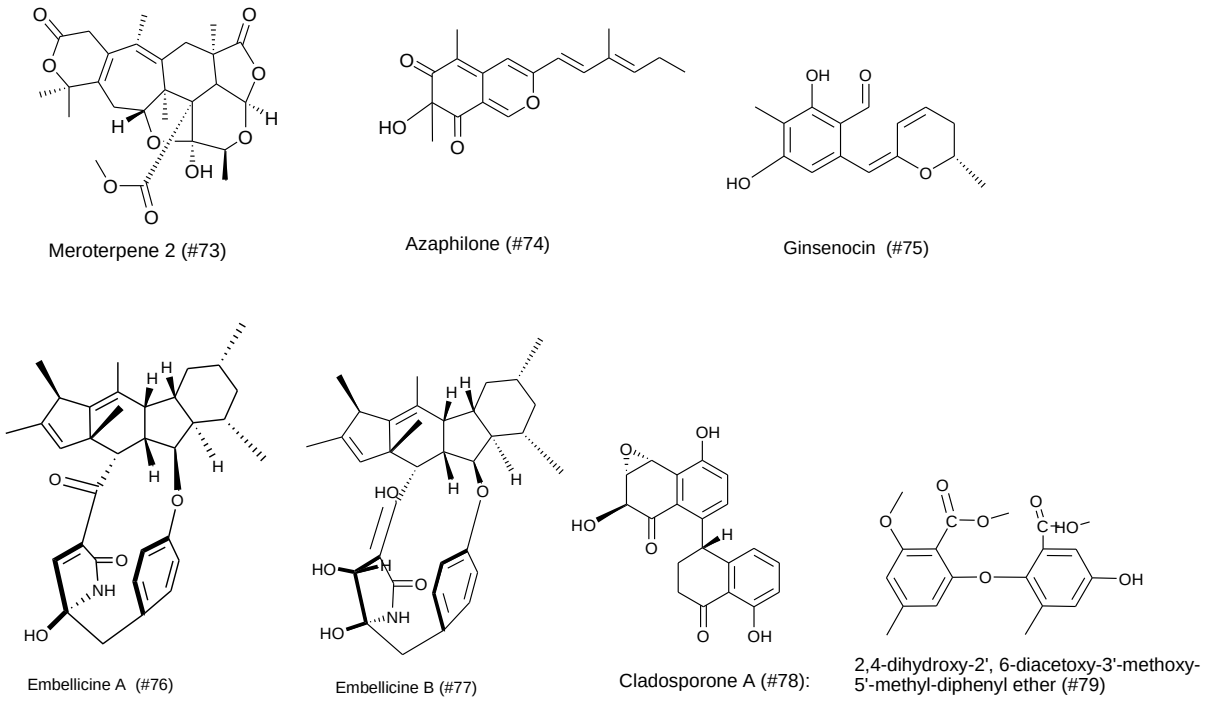


Fig. (4). Structures of Novel anticancer metabolites isolated from Hyphomycetes (#73-#79).

from the flower of the mangrove plant *Kandelia candel*, collected at Daya Bay, Shenzhen city, Guangdong province, China. Cladosporone A exhibited moderate cytotoxic effect towards human tumor cell lines K562, A549, HL-60, Huh-7, MCF-7, H1975, U937, BGC823, Hela and MOLT-4 with IC_{50} values ranging from 10 to 53.7. Moreover, in anti-COX-2 (human recombinant COX-2) assay, Cladosporone A (#78) and showed inhibitory activities with IC_{50} values of 49.1 [61].

Compound, 2, 4-dihydroxy-2', 6-diacetoxy-3'-methoxy-5'-methyl-diphenyl ether (#79 in Fig. **4**) which is a new diphenyl ether was isolated from an endophytic fungus *Verticillium* sp. from roots of *Rehmannia glutinosa,*, from Wushe County, Henan Province, China. The compound showed cytotoxic activity against HL-60 cell lines (IC_{50} 2.24 μg/mL) [62].

5. CONCLUSION AND FUTURE PROSPECTS

Access to limited number of cancer chemotherapies, their potential side effects and high cost makes the treatment of cancer a challenging issue. Further, many therapies do not treat cancers effectively and the multi-drug-resistance against already known compounds intensifies this complexity. Therefore, considering the number of cancer related deaths per year continuous search for new sources of cost-effective natural products with anticancer properties is a necessity. It has been observed that certain microorganisms inhabit interesting niches such as the interstitial spaces of healthy plants and exhibit complex interactions with their host. These endophytes have the ability to synthesize secondary metabolites with significant and novel characteristics that can be adapted for medicinal use. A large number of them producing novel bioactive compounds have been isolated from endophytic fungi. Moreover, the ability of endophytic fungi to produce phytochemicals originally produced by host plants adds to the benefits of using these microorganisms.

In future, genetic engineering, improved cultivation and fermentation techniques will allow researchers to isolate new endophytic fungal strains producing antitumor compounds. Moreover, deciphering and manipulations of novel metabolic pathways for mass production of anticancer compounds will be a critical step for development of cost effective cancer treatment. Our understanding of the mechanisms involved with cancer development is increasing and this information can be used to select potent compounds with anticancer activity. Research focus on molecular characterization of endophytes and optimization of culture conditions will improve the chances of success in new drug discovery efforts. Thus, endophytic fungi will continue to be a promising source of unexplored secondary metabolites and may be exploited further for discovery of new drugs for cancer treatment.

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REFERENCES

[1] Wrigley S. Biodiversity: New leads for the pharmaceutical and agrochemical industries: Royal Society of Chemistry; 2000.

[2] Stierle A, Strobel G, Stierle D. Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science 1993;260(5105):214-6.

[3] Schulz B, Boyle C, Draeger S, Römmert A-K, Krohn K. Endophytic fungi: a source of novel biologically active secondary metabolites. Mycol Res2002;106(09):996-1004.

[4] Strobel G, Daisy B, Castillo U, Harper J. Natural products from endophytic microorganisms⊥. J Nat Prod 2004;67(2):257-68.

[5] Kharwar RN, Mishra A, Gond SK, Stierle A, Stierle D. Anticancer compounds derived from fungal endophytes: their importance and future challenges. Nat Product Rep 2011;28(7):1208-28.

[6] Deshmukh SK, Verekar SA. Fungal Endophytes: An Amazing and Hidden Source of Cytotoxic Compounds. Microbial Diversity and Biotechnology in Food Security: Springer; 2014. p. 59-89.

[7] Puri SC, Verma V, Amna T, Qazi GN, Spiteller M. An Endophytic Fungus from ~~Nothapodytes f oetida~~, that Produces Camptothecin. J Nat Prod 2005;68(12):1717-9.

[8] Rehman S, Shawl A, Kour A, *et al*. An endophytic Neurospora sp. from Nothapodytes foetida producing camptothecin. App Biochem Microbiol 2008;44(2):203-9.

[9] Kusari S, Zühlke S, Spiteller M. An endophytic fungus from Camptotheca acuminata that produces camptothecin and analogues. J Nat Prod 2009;72(1):2-7.

[10] ~~Eyberger AL, Dondapati R, Porter JR. Endophyte fungal isolates from Podophyllum peltatum produce podophyllotoxin. J Nat Prod 2006;69(8):1121-4.~~

[11] Puri SC, Nazir A, Chawla R, *et al*. The endophytic fungus Trametes hirsuta as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. J Biotechnol 2006;122(4):494-510.

[12] Wang Y, Xu L, Ren W, Zhao D, Zhu Y, Wu X. Bioactive metabolites from Chaetomium globosum L18, an endophytic fungus in the medicinal plant Curcuma wenyujin. Phytomedicine 2012;19(3):364-8.

[13] Du X-P, Su W-J. Two New Polyketides from Mangrove Endophytic Fungus sp. Chem Nat Comp 2014;2(50):214-6.

[14] El Amrani M, Lai D, Debbab A, *et al*. Protein kinase and HDAC inhibitors from the endophytic fungus Epicoccum nigrum. J Nat Prod 2013;77(1):49-56.

[15] Zhang D, Ge H, Xie D, *et al*. Periconiasins A–C, New Cytotoxic Cytochalasans with an Unprecedented 9/6/5 Tricyclic Ring System from Endophytic Fungus Periconia sp. Org lett 2013;15(7):1674-7.

[16] Li X, Tian Y, Yang S-x, Zhang Y-m, Qin J-c. Cytotoxic azaphilone alkaloids from Chaetomium globosum TY1. Bioorg Med Chem Lett 2013;23(10):2945-7.

[17] Ortega HE, Graupner PR, Asai Y, TenDyke K, Qiu D, Shen YY, et al. Mycoleptodiscins A and B, cytotoxic alkaloids from the endophytic fungus Mycoleptodiscus sp. F0194. J Nat Prod 2013;76(4):741-4.

[18] Yan HJ, Li XM, Li CS, Wang BG. Alkaloid and Anthraquinone Derivatives Produced by the Marine-Derived Endophytic Fungus Eurotium rubrum. Helvetica Chimica Acta 2012;95(1):163-8.

[19] Verekar SA, Mishra PD, Sreekumar ES, *et al*. Anticancer activity of new depsipeptide compound isolated from an endophytic fungus. The J Antibiot 2014; 67(10):697-701.

[20] Yang X-L, Li Z-Z. New spiral γ-lactone enantiomers from the plant endophytic fungus Pestalotiopsis foedan. Molecules 2013;18(2):2236-42.

[21] Ding G, Qi Y, Liu S, Guo L, Chen X. Photipyrones A and B, new pyrone derivatives from the plant endophytic fungus Pestalotiopsis photiniae. The J Antibiot 2012;65(5):271-3.

[22] Lin T, Wang G, Shan W, *et al*. Myrotheciumones: Bicyclic cytotoxic lactones isolated from an endophytic fungus of Ajuga decumbens. Bioorg Med Chem Lett 2014;24(11):2504-7.

[23] Zhang W, Xu L, Yang L, Huang Y, Li S, Shen Y. Phomopsidone A, a novel depsidone metabolite from the mangrove endophytic fungus Phomopsis sp. A123. Fitoterapia 2014;96:146-51.

[24] Adames I, Ortega HE, Asai Y, *et al*. 3-epi-Waol A and Waol C: polyketide-derived γ-lactones isolated from the endophytic fungus Libertella blepharis F2644. Tetrahedron Lett 2015;56(1):252-5.

[25] Yuan L, Huang W, Du G, *et al*. Isolation of Xanthones from the Fermentation Products of the Endophytic Fungus of Phomopsis amygdali. Chem Nat Comp 2015;51(3):460-3.

[26] Yang H-Y, Gao Y-H, Niu D-Y, *et al*. Xanthone derivatives from the fermentation products of an endophytic fungus Phomopsis sp. Fitoterapia.2013;91:189-93.

[27] Huang Z, Yang J, Lei F, She Z, Lin Y. A New Xanthone O-Glycoside from the Mangrove Endophytic Fungus Phomopsis sp. Chem Nat Comp 2013;49(1):27-30.

[28] Li H, Huang H, Shao C, *et al*. Cytotoxic norsesquiterpene peroxides from the endophytic fungus Talaromyces flavus isolated from the mangrove plant Sonneratia apetala. J Nat Prod. 2011;74(5):1230-5.

[29] Shang Z, Li XM, Li CS, Wang BG. Diverse Secondary Metabolites Produced by Marine-Derived Fungus Nigrospora sp. MA75 on Various Culture Media. Chem Biodiversity 2012;9(7):1338-48.

[30] Hemtasin C, Kanokmedhakul S, Kanokmedhakul K, *et al*. Cytotoxic pentacyclic and tetracyclic aromatic sesquiterpenes from Phomopsis archeri. J Nat Prod 2011;74(4):609-13.

[31] Wijeratne EK, Bashyal BP, Liu MX, *et al*. Geopyxins A–E, ent-Kaurane Diterpenoids from Endolichenic Fungal Strains Geopyxis aff. majalis and Geopyxis sp. AZ0066: Structure–Activity Relationships of Geopyxins and Their Analogues (1). J Nat Prod 2012;75(3):361-9.

[32] Feng Y, Ren F, Niu S, *et al*. Guanacastane diterpenoids from the plant endophytic fungus Cercospora sp. J Nat Prod 2014;77(4):873-81.

[33] Sun J-F, Lin X, Zhou X-F, *et al*. Pestalols A–E, new alkenyl phenol and benzaldehyde derivatives from endophytic fungus Pestalotiopsis sp. AcBC2 isolated from the Chinese mangrove plant Aegiceras corniculatum. The J Antibiot 2014;67(6):451-7.

[34] Liu L, Li Y, Li L, *et al*. Spiroketals of Pestalotiopsis fici provide evidence for a biosynthetic hypothesis involving diversified Diels–Alder reaction cascades. The J Org Chem 2013;78(7):2992-3000.

[35] Liu L, Bruhn T, Guo L, *et al*. Chloropupukeanolides C–E: cytotoxic pupukeanane chlorides with a spiroketal skeleton from Pestalotiopsis fici. Chem-A Eur J 2011;17(9):2604-13.

[36] Ding G, Zhang F, Chen H, Guo L, Zou Z, Che Y. Pestaloquinols A and B, isoprenylated epoxyquinols from Pestalotiopsis sp. J NatProd 2011;74(2):286-91.

[37] Zang L-Y, Wei W, Wang T, Guo Y, Tan R-X, Ge H-M. Isochromophilones from an endophytic fungus Diaporthe sp. Nat Prod Bioprospecting 2012;2(3):117-20.

[38] Chen Z-m, Chen H-P, Li Y, Feng T, Liu J-K. Cytochalasins from cultures of endophytic fungus Phoma multirostrata EA-12. The J Antibiot 2014.

[39] Song Y, Dou H, Wang P, *et al*. A novel small-molecule compound diaporine A inhibits non-small cell lung cancer growth by regulating miR-99a/mTOR signaling. Cancer Biol Ther 2014;15(10):1423-30.

[40] Xu Y-m, Espinosa-Artiles P, Liu MX, Arnold AE, Gunatilaka AL. Secoemestrin D, a Cytotoxic Epitetrathiodioxopiperizine, and Emericellenes A–E, Five Sesterterpenoids from Emericella sp. AST0036, a Fungal Endophyte of Astragalus lentiginosus 1. J Nat Prod 2013;76(12):2330-6.

[41] Lu S, Kurtán T, Yang G, *et al*. Cytospolides A–E, New Nonanolides from an Endophytic Fungus, Cytospora sp. Eur J Org Chem 2011;2011(28):5452-9.

[42] Wibowo M, Prachyawarakorn V, Aree T, *et al*. Tricyclic and Spirobicyclic Norsesquiterpenes from the Endophytic Fungus Pseudolagarobasidium acaciicola. Eur J Org Chem 2014;2014(19):3976-80.

[43] Wu L-S, Hu C-L, Han T,, *et al*. Cytotoxic metabolites from Perenniporia tephropora, an endophytic fungus from Taxus chinensis var. mairei. App Microbiol Biotechnol 2013;97(1):305-15.

[44] Ligon BL, editor Penicillin: its discovery and early development. Seminars in pediatric infectious diseases; 2004: Elsevier.

[45] Cao P, Yang J, Miao CP, *et al*. New duclauxamide from Penicillium manginii YIM PH30375 and structure revision of the duclauxin family. Org Lett 2015;17(5):1146-9.

[46] Gao S-S, Li X-M, Du F-Y, Li C-S, Proksch P, Wang B-G. Secondary metabolites from a marine-derived endophytic fungus Penicillium chrysogenum QEN-24S. Marine Drugs 2010;9(1):59-70.

[47] Meléndez-González C, Murià-González MJ, Anaya AL, Hernández-Bautista BE, Hernández-Ortega S, González MC. Acremoxanthone E, a Novel Member of Heterodimeric Polyketides with a Bicyclo [3.2. 2] nonene Ring, Produced by Acremonium camptosporum W. Gams (Clavicipitaceae) Endophytic Fungus. Chem Biodiversity 2015;12(1):133-47.

[48] Zhou M, Miao MM, Du G, Li XN, Shang SZ, Zhao W. Aspergillines A-E, highly oxygenated hexacyclic indole-tetrahydrofuran-tetramic acid derivatives from Aspergillus versicolor. Org Lett 2014;16(19):5016-9.

[49] Meng L-H, Li X-M, Lv C-T, Huang C-G, Wang B-G. Brocazines A–F, cytotoxic bisthiodiketopiperazine derivatives from Penicillium brocae MA-231, an endophytic fungus derived from

the marine mangrove plant Avicennia marina. J NatProd 2014;77(8):1921-7.

[50] Huang CH, Pan JH, Chen B, Yu M, Huang HB, Zhu X. Three bianthraquinone derivatives from the mangrove endophytic fungus Alternaria sp. ZJ9-6B from the South China Sea. Mar Drugs 2011;9(5):832-43.

[51] Mohamed HF. Molecular analysis and anticancer properties of two identified isolates, Fusarium solani and Emericella nidulans isolated from Wady El-Natron soil in Egypt against Caco-2 (ATCC) cell line. Asian Pacific J Tropical Biomed 2012;2(11):863-9.

[52] Metwaly AM, Fronczek FR, Ma G, Kadry HA, El-Hela AA, Mohammad A-EI. Antileukemic α-pyrone derivatives from the endophytic fungus Alternaria phragmospora. Tetrahedron Lett 2014;55(24):3478-81.

[53] Liu D, Li XM, Meng L, Li CS, Gao SS, Shang Z. Nigerapyrones A-H, alpha-pyrone derivatives from the marine mangrove-derived endophytic fungus Aspergillus niger MA-132. J Nat Prod 2011;74(8):1787-91.

[54] Li C, Gong B, Cox DG, Li C, Wang J, Ding W. Dichlorodiaportinol A–A new chlorine-containing isocoumarin from an endophytic fungus Trichoderma sp. 09 from Myoporum bontioides A. Gray and its cytotoxic activity. Pharmacog Maga 2014;10(Suppl 1):S153.

[55] Kornsakulkarn J, Dolsophon K, Boonyuen N, Boonruangprapa T, Rachtawee P, Prabpai S. Dihydronaphthalenones from endophytic fungus Fusarium sp. BCC14842. Tetrahedron 2011;67(39):7540-7.

[56] Budhiraja A, Nepali K, Sapra S, Gupta S, Kumar S, Dhar KL. Bioactive metabolites from an endophytic fungus of Aspergillus species isolated from seeds of Gloriosa superba Linn. Medl Chem Res 2013;22(1):323-9.

[57] Gu W, Qiao C. Furandiones from an Endophytic Aspergillus terreus Residing in Malus halliana. Chem Pharmaceutical Bulletin 2012;60(11):1474-7.

[58] Li J, Yang X, Lin Y, Yuan J, Lu Y, Zhu X.Meroterpenes and azaphilones from marine mangrove endophytic fungus Penicillium 303#. Fitoterapia 2014;97:241-6.

[59] Zheng C-J, Xu L-L, Li Y-Y, Han T, Zhang Q-Y, Ming Q-L.Cytotoxic metabolites from the cultures of endophytic fungi from Panax ginseng. App Microbiol Biotechnol 2013;97(17):7617-25.

[60] Ebrahim W, Aly AH, Wray V, Mándi A, Teiten M-Hln, Gaascht Fo. Embellicines A and B: Absolute configuration and NF-κB transcriptional inhibitory activity. J Med Chem 2013;56(7):2991-9.

[61] Ai W, Lin X, Wang Z, Lu X, Mangaladoss F, Yang X. Cladosporone A. A new dimeric tetralone from fungus Cladosporium sp. KcFL6'derived of mangrove plant Kandelia candel. The J Antibiot 2014.

[62] Wei P, Fei Y, Xiao-Li L, Min J, ZHENG C-J, Ting H. A new diphenyl ether from the endophytic fungus Verticillium sp. isolated from Rehmannia glutinosa. Chin J Nat Med 2013;11(6):673-5.