Natural Products with Antitumor Activity from Endophytic Fungi

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Abstract: Endophytic fungi are a seemingly inexhaustible source of novel bioactive natural products. Currently, more than 140 fungal metabolites have shown confirmed activity in tumor cell line bioassays. We present the chemical structures of these antitumor metabolites, their corresponding fungal endophytes and host plants, and the activities they exhibited, and briefly discuss some of their action mechanisms. This review emphasizes the role of endophytic fungi as an important source of leads for drug discoveries.

Keywords: Antitumor activity, fungal endophytes, natural products, secondary metabolites.

1. INTRODUCTION

Despite the current focus on synthetic products, natural products are a continuing source of novel bioactive metabolites, retaining an immense impact on modern medicine. From 1981 to 2006, about 68% of antibacterial compounds and 34% of products used in cancer therapy were either natural products themselves or direct derivatives [1].

Fungal endophytes are microorganisms that colonize living internal tissues of plants without causing disease symptoms [2]. Notably, each of the nearly 300,000 known plant species hosts one or more fungal endophytes. Endophytic fungi are thought to contribute to their host plant by producing a plethora of substances that provide protection and survival value to the plant [3]. Fungal endophytes appear to be an inexhaustible source of novel bioactive natural products.

Although the first endophytic fungi were isolated from the seed of *Lolium temuleatum* more than 100 years ago, the study of fungal endophytes took off in 1993 with the pioneering work of Stierle *et al.* [4], who discovered the taxol- and taxane-producing fungal endophyte *Taxomyces andreanae* in the Pacific yew (*Taxus brevifolia*). This discovery provided not only a novel alternative method of exploring therapeutically useful compounds from nature but also a way to protect limited plant resources worldwide. Since then, a great number of novel compounds have been isolated from fungal endophytes with a range of biological activities, including antifungal [5-6], antibacterial [7-8], immunosuppressive [9], anti-HIV [10-11], antioxidant [12-13] and insulin-receptor activation activities [14], to name a few. Fungal endophytes are also a prolific source of novel antitumor compounds. Some of these products have the same chemical structures as metabolites of their host plants; others are quite different. Among examples of endophytic metabolites with antitumor activities that have been isolated in recent years are important anticancer leads, such as taxol, camptothecin, and podophyllotoxin, as well as the fungal endophyte-specific metabolites cytochalasins, which are further described below.

This article reviews isolated natural products from endophytic fungi with antineoplastic activities. The products are classified by their chemical structure. The corresponding endophytic fungi and host plants, exhibited activities, and some action mechanism of the metabolites are also discussed here, with references to the original articles.

2. ANTITUMOR METABOLITES FROM FUNGAL ENDOPHYTES

More than 140 natural products with different levels of antitumor activity have been isolated from fungal endophytes. These products can be grouped into several categories: terpenoids, alkaloids, quinones, flavonoids, isocoumarins and lignans, lactones and esters, peptides, and miscellaneous metabolites. Following are descriptions of the types of antitumor metabolites which were isolated from fungal endophytes.

2.1. Terpenoids

Terpenoids with antitumor activity have been isolated from a variety of endophyte cultures originating from different host plants. Those identified so far are mainly sesquiterpenes and diterpenes.

2.1.1. Sesquiterpenes

Four sesquiterpenoids, 8-deoxy-trichothecin **1**, trichothecolone **2**, 7α-hydroxytrichodermol **3** and 7α-hydroxyscirpene **4** were isolated from an endophytic fungus belonging to order Hypocreales in the twig of *Knema laurina* (Blume) Warb. Compounds **1** and **3** showed highly antitumor activities against BC-1 (Human breast cancer, IC_{50}

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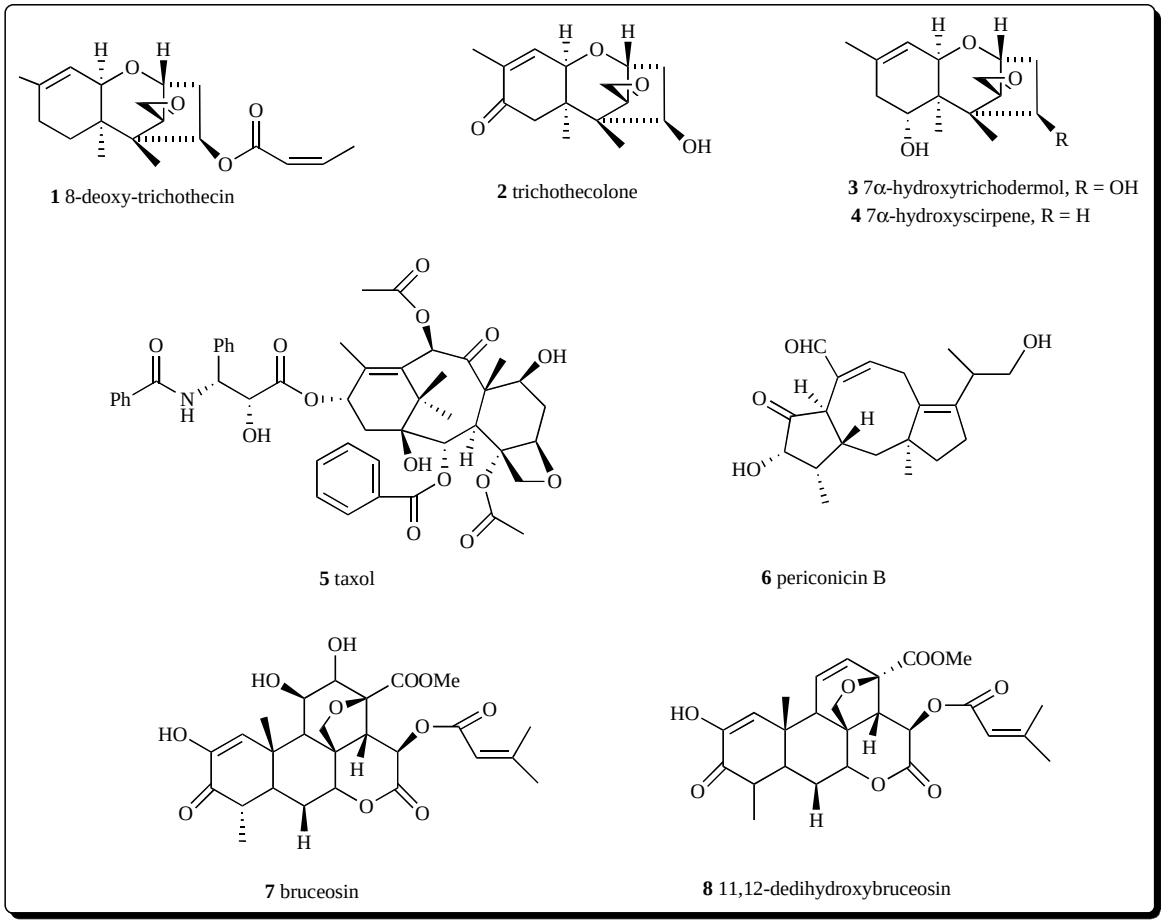


0.88, 2.37μM) and NCI-H187 (Human small cell lung cancer, IC_{50} 1.48, 1.37 μM) cells. While compounds **2** and **4** were moderately active against BC-1 (IC_{50} 10.06, 21.53 μM), NCI-H187 (IC_{50} 11.31, 27.76 μM) and KB (Human epidermoid carcinoma of the mouth cells, IC_{50} 12.90, 8.47 μM) [15].

2.1.2. Diterpenes

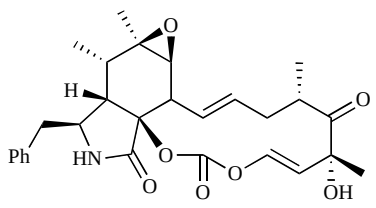
Taxol **5**, a microtubule inhibitor, is a highly efficient, low-toxicity, and broad-spectrum natural anticancer drug widely used in treatment of breast, uterine and other cancers [16]. This highly functionalized diterpenoid is found in extremely small quantities in all *Taxus* species. The endophytic fungus *Taxomyces andreanae* was originally isolated from the inner bark of Pacific yew (*Taxus brevifolia*) by Stierle and coworkers [4]. They characterized the fungus and found that it produced taxol. This report led to a novel alternative method for producing taxol. Isolation of this compound from endophytic fungi and search for new taxol-producing fungi prompted intensive investigations. Recent review articles have presented comprehensive accounts of relevant work [17-18]. These studies have also indicated that traditional pharmaceutical plants are a good source of antitumor metabolite-producing endophytes. Periconicin B **6** is a diterpene first isolated from an endophytic fungus *Periconia* sp. in small branches of *Taxus cuspidate* [19] and then it was isolated by Helder and coworkers [20] from *Periconia atropurpurea* in the leaves of *Xylopia aromatica*, a native plant of the Brazilian Cerrado. Biological analysis showed that it had potent cytotoxicity against two cancer cell lines, HeLa (human cervix carcinoma) and CHO (Chinese hamster ovary), both with IC_{50} values of 8.0 μM. Bruceosin **7** and 11,12-dedihydroxybruceosin **8** were obtained as a mixture from an endophytic fungus *Fusarium chlamydosporum* in fruits of *Brucea javanica* collected from Cianjur, West Java. The mixture showed cytotoxic effects against L1210 (leukemia cells) with an IC_{50} of 4.29 μg/mL [21].

2.2. Alkaloids

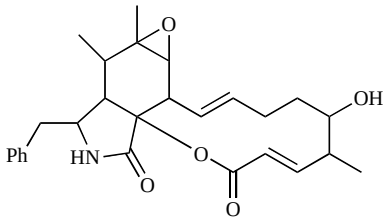
Endophytic fungi commonly contain alkaloids, which play an important role in inhibiting herbivores and insects. The types and levels of alkaloids appear to depend more on the species, strain, or genotype of the endophyte and less on the host grass genotype or environment [22]. Fungal genera such as *Xylaria*, *Phoma*, *Hypoxylon*, *Chaetomium* and *Stachybotrys* etc. are the most promising producers of bioactive compounds, such as cytochalasins [2, 10]. Alkaloids from fungal endophytes include indole derivatives, amides and quinolines etc.

2.2.1. Indole Derivatives

Indole derivatives are common substances produced by fungal endophytes that comprise nearly 60% of alkaloids with known antitumor activity. Among them, the cytochalasins have generated much interest because of their



9 cytochalasin E



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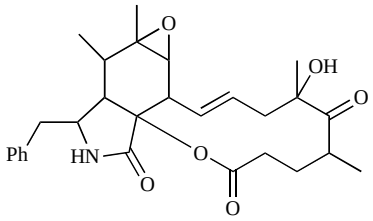

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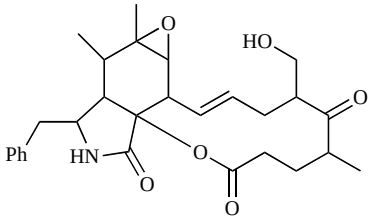

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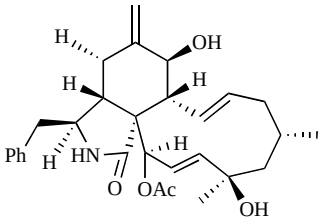
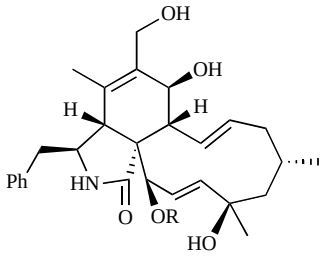
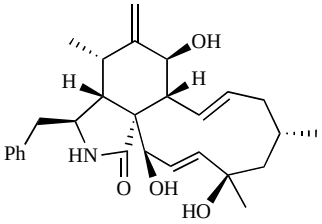


13 cytochalasin H

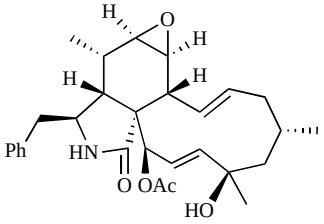


14 cytochalasin Z10, R = H

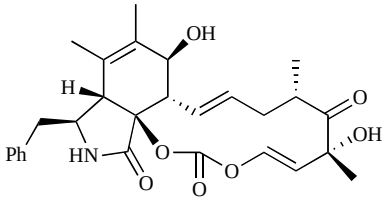
15 cytochalasin Z11, R = Ac



16 cytochalasin J



17 epoxycytochalasin H



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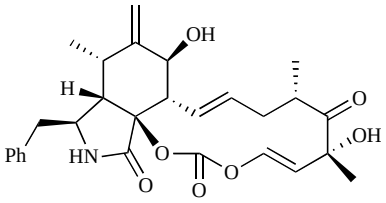

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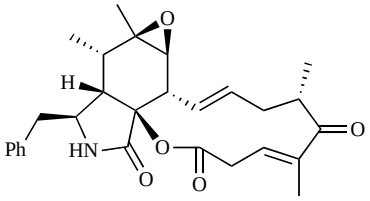
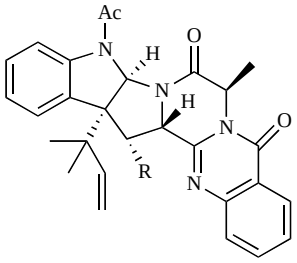
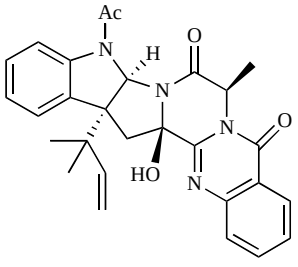


20 rosellichalasin



21 R = OH

22 R = H



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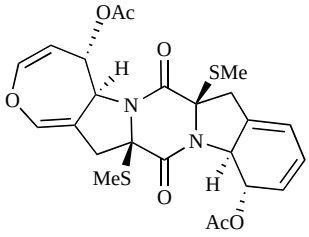


24 acetylapoaranotin

broad spectrum of antitumor activities. Cytochalasins were first isolated and characterized by Aldridge and Turner [23-24] at imperial Chemical Industries and have since been identified as metabolites of a number of fungi. Four cytochalasins **9-12** have been separated from a fungal strain in the genus *Rhinocladiella* residing in the medicinal plant *Tripterygium wilfordii*. A bioassay for cytotoxicity showed cytochalasin E **9** to be significantly active against three tested human tumor cell lines 2780S (IC_{100} < 0.0153 μg/mL), SW-620 (colon tumor cell lines, IC_{100} = 0.244 μg/mL) and HCT-116 (IC_{100} = 0.977 μg/mL), respectively, while compounds **10-12** showing only weak to moderate cytotoxicity [25]. The action mechanism of cytochalasin E was inhibition of actin filament elongation by binding to high affinity sites located at the polymerization end of the filament [26].

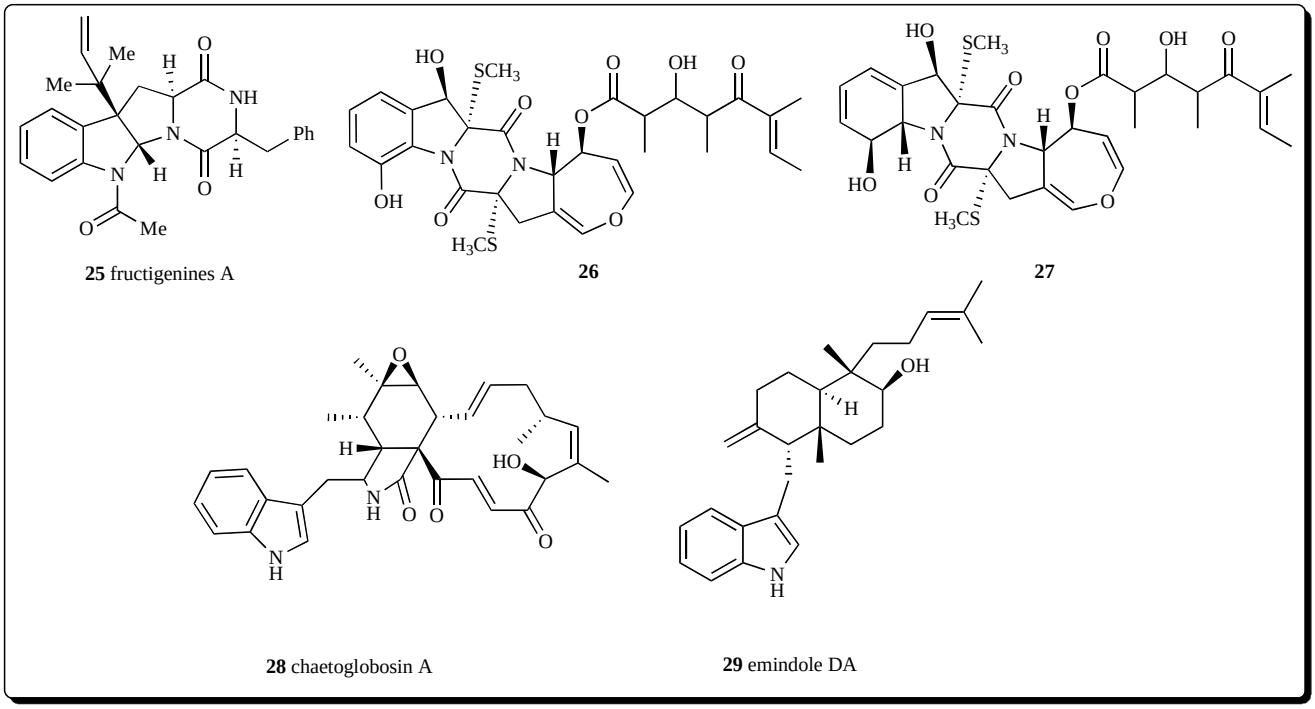
Cytochalasin H **13** was another cytochalasin metabolite isolated from the mangrove fungal endophyte *Phomopsis* sp. (ZZF08) in the South China Sea coast. Cytochalasin H exhibited potent cytotoxicity towards KB and KBv 200 cells with IC_{50} less than 1.25 μg/mL [27]. Cytochalasin Z10 (**14)** and Z11 (**15)** were isolated together with cytochalasin H **13**, cytochalasin J **16** and epoxycytochalasin H **17** from *Endothia gyrosa* IFB-E023 in the leaf of *Vatica mangachapo*. All these compounds were demonstrated to be substantially cytotoxic against the human leukaemia K562 cell line with the IC_{50} values of 10.1, 1.5, 24.5, 28.3, and 24.4 μM, respectively [28]. Four cytochalasins, cytochalasin E **(9**), 5, 6-dehydro-7-hydroxycytochalasin E **18**, Δ6,12-isomer of **18** (**19**) and rosellichalasin **20** were elaborated by *Aspergillus sterreus.* Moreover, a new diketopiperazine derivative, named 16α-hydroxy-5*N*-acetylardeemin **21** along with three known analogues, 5*N*-acetylardeemin **22**, 15b-β-hydroxy-5*N*-acetylardeemin **23**, acetylapoaranotin **24** were also detected in the culture of *A. sterreus.* All compounds showed moderate to weak cytotoxic activity against KB and HSC‑T6 cell lines [29].

Fructigenines A **25** was a diketopiperazine alkaloid separated from the endophytic *Penicillium auratiogriseum* derived from sponge *Mycale plumose* by bioassay-guided fractionation and showed potent cytotoxic effect against tsFT210 (the mouse cdc2 mutant cell), with maximum inhibitory effect observed at 22.0 μg/mL [30]. Two dithiodiketopiperazines **26**, **27** were isolated from the seed fungus *Menisporopsis theobromae* BCC3975 and showed cytotoxicity against NCI-H187 cell line with IC_{50} value of 22.9, 20.3 μM, respectively. Moreover, compound **27** exhibited cytotoxicity against BC-1 cell lines with IC_{50} value of 2.95 μM [31].

Chaetoglobosins are cytochalasan-based alkaloids mainly produced by *Chaetomium globosum* [32-34]. Chaetoglobosin A **28** was an antitumor metabolite first identified from *Chaetomium* spp. in 1982 [35]. Zhang and coworkers also purified chaetoglobosin A from the endophytic fungus *Chaetomium globosum* in the stem and leaf of *Maytenus hookeri*, which was different from the anticancer product maytensine produced by the host plant [36]. Emindole DA **29** was an indole alkaloid from marine-derived fungus *Emericella nidulans* var. *acristata* in a green alga collected around Sardinia in the Mediterranean Sea. It displayed antitumor activity in a panel of 36 human tumor cell lines, exhibiting a mean IC_{50} value of 5.5 μg/mL *in vitro* survival and proliferation assay [37].

2.2.2. Amides

TAN-1813 (**30**), a maleic acid amide derivative, was isolated from the culture broth of endophytic *Phoma* sp. FL-41510. The compound inhibited the proliferation to various human cancer cells *in vitro* with IC_{50} values of 15~110



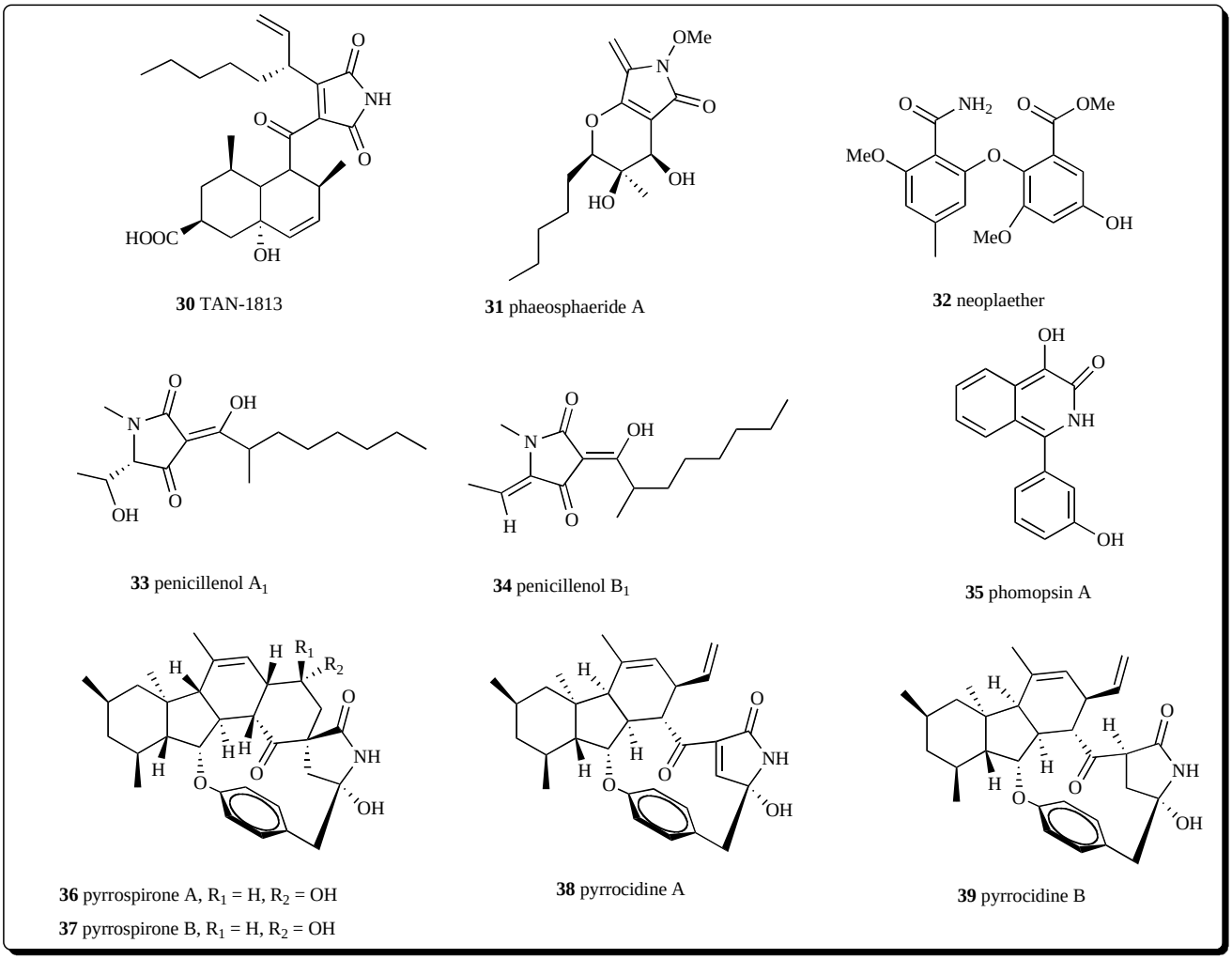
25 fructigenines A **26** **27**

28 chaetoglobosin A **29** emindole DA

ng/mL. It also inhibited human fibrosarcoma HT-1080 and NIH3T3/K-ras tumors *in vivo*. TAN-1813 is a novel farnesyl-protein transferase (FPTase) inhibitor; it inhibited rat brain farnesyltransferase and geranylgeranyltransferase I with IC_{50} values of 23 μg/mL and 47 μg/mL, respectively. TAN-1813 inhibited farnesylpyrophosphate and a K-Ras C-terminal peptide [38]. Phaeosphaeride A **31** is anitrogen-containing bicyclic compound produced by the endophytic fungus isolated from plant collected in the Archbold Biological Station, a 5000-acre preserve in Lake Placid, Florida. It inhibited signaling by the signal transducer and activator of transcription (STAT) 3 both *in vitro* and *in vivo* in ELISA-based screen with IC_{50} of 0.61 mM and 6.7 μM, respectively [39]. A new metabolite neoplaether **32** was characterized from an endophytic strain of *Neoplaconema napellum* IFB-E016 in *Hopea hainanensis*. It exhibited significant cytotoxic activity to KB cell line, with an IC_{50} value of 13.0 μg/mL [40]. The two amides, penicillenols A_1 (**33**) and B_1 (**34**) were characterized as decalin tetramic acid type derivatives, which were elaborated by *Penicillium* sp. GQ-7, an endophytic fungus associated with *Aegiceras corniculatum*. Both two compounds exhibited inhibitory activity against HL-60 cell line with IC_{50} values of 0.76 μM and 3.20 μM, respectively [41]. In addition to cytochalasin H, a new alkaloid phomopsin A **35** was also obtained from *Phomopsis* sp. (ZZF08) and had moderate cytoxicity towards KB and KBv 200 cells with IC_{50} of 28.0 and 16.8 μg/mL, respectively [27]. Pyrrospirones A **36** and B **37** with two known compounds pyrrocidines A **38** and B **39** were metabolised by *Neonectria ramulariae* Wollenw KS-246, an endophytic fungus obtained from a branch collected from Mt. Gassan, Yamagata, Japan. All these compounds exhibited cytotoxicity *in vitro* against HL-60, K562 and LNCaP (human chronic myelogenous leukemia) cell lines with IC_{50} values ranging from 0.12 to 20.24 μM [42].

2.2.3. Quinolines

Camptothecin (CPT, **40**) is a naturally occurring pentacyclic quinoline alkaloid. CPT has effect on lung, ovarian and uterine cancers [43]. CPT interferes with mammalian DNA topoisomerase I by trapping a reversible enzyme-DNA cleavable complex [44-45]. It was first identified by Wall and coworkers [46] from the wood of *Camptotheca acuminate* (Nyssaceae), a native Chinese plant. Recently, it was obtained too, from a fungal endophyte *Entrophospora infrequens* isolated from an anticancer medicinal plant *Nothapodytes foetida* in the Western coast of India [47]. Asperfumoid **41** was a quinoline alkaloid first characterized as an antibiotic from *Aspergillus fumigatus* CY018 residing in the leaf of *Cynodon dactylon* [48] and



30 TAN-1813

31 phaeosphaeride A

32 neoplaether

33 penicillenol A_1

34 penicillenol B_1

35 phomopsin A

36 pyrrospirone A, R_1 = H, R_2 = OH

37 pyrrospirone B, R_1 = H, R_2 = OH

38 pyrrocidine A

39 pyrrocidine B

then purified from the culture of *Penicillium* sp. in the leaf of *Hopea hainanensis*. It exhibited cytotoxic activity against KB and HepG2 cell lines with IC_{50} value of 20.0 and 15.0 μg/mL, respectively [49].

2.2.4. Others

Jiao and coworkers characterized a novel alkaloid with a new framework, namely chaetominine **42** from the solid-substrate culture of *Chaetomium* sp. IFB-E015 in *Adenophora axilliflora* leaves. It exhibited strong cytotoxic activity *in vitro* against human leukemia K562 and colon cancer SW1116 cell lines with IC_{50} values of 21.0 and 28.0 nM, more potent than those (33.0 and 76.0 nM, respectively) of 5-fluorouracil co-tested as a positive reference [50]. Chaetoglobin A **43** was an unusual azaphilone alkaloid from endophytic *Chaetomium globosum* residing in *Imperata cylindrical*, it inhibited the proliferation of MCF-7 (human breast cancer cell line) and SW1116 (colon cancer cell line) with IC_{50} values of 26.8 and 35.4 μg/mL, respectively. It also inhibited expressions of tumor-related genes bcl-2, c-myc and β-catenin [51]. In addition to two dithiodiketopiperazine derivatives (compounds **26** and **27),** a new alkaloid 5-benzyl-1-hydroxy-3-(hydroxyphenylmethylene)-3H-pyrazine-2,6-dione **44** was also isolated from the seed fungus *Menisporopsis theobromae* BCC3975 and showed toxicity to the NCI-H187 and BC-1cell lines with IC_{50} values of 57.4 and 1.8 μM, respectively [31].

2.3. Quinones

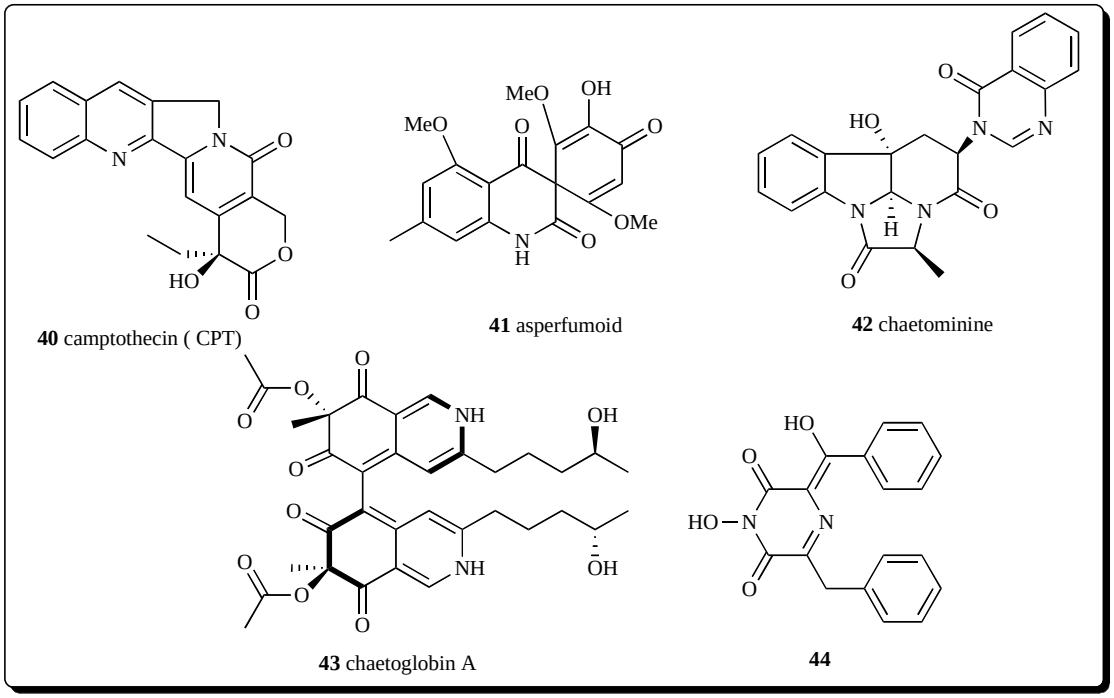
A number of quinone derivatives produced by fungal endophytes have been reported with potent inhibition of tumor cell lines. They involve benzoquinones, naphthoquinones and anthraquinones. Some of which are analogues arising from metabolic degradation of quinone skeletons.

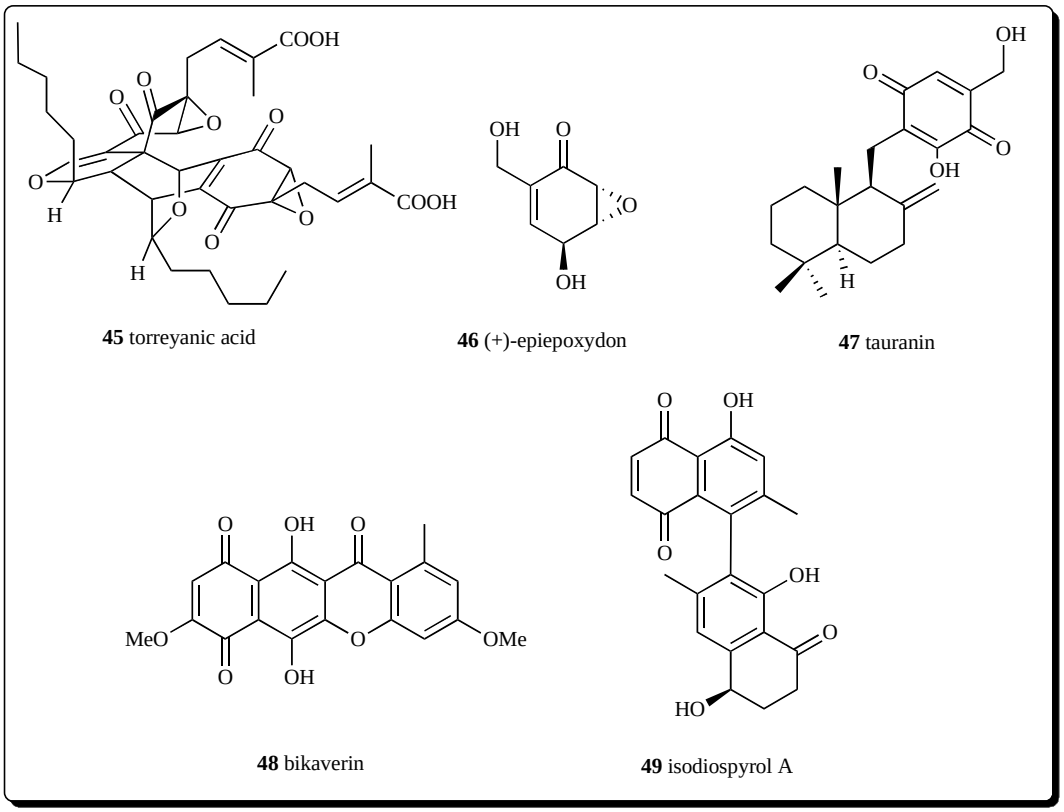
2.3.1. Benzoquinones

Torreyanic acid **45**, an unusual dimeric benzoquinone was elaborated by *Pestalotiopsis microspora* presented in *Torreya taxifolia*, an endangered species closely related to the taxol-producing Pacific yew (*Taxus brevifolia*). It was cytotoxicity against a panel of 25 human cancer cell lines with a mean IC_{50} value of 9.4 μg/mL [52]. Klemke and coworkers isolated (+)-epiepoxydon **46** from the marine fungus *Apiospora montagnei* in the inner tissue of the North Sea alga *Polysiphonia violacea*. It displayed strongly cytotoxicity against HM02, HepG2, and MCF7 human cancer cell lines with GI_{50} values of 0.7, 0.75 and 0.8 μg/mL, respectively [53]. Tauranin **47** was a sesquiterpene quinone exhibited in *Phyllosticta spinarum* from *Platycladus orientalis*. It showed antiproliferative activity *in vitro* against five sentinel cancer cell lines including NCI-H460 (non small cell lung), MCF-7 (breast), SF-268(CNS glioma), PC-3M (prostate) and MIA Pa Ca-2 (pancreatic) with IC_{50} range from 1.5 to 4.3 μM. The compound **47** induced accumulation of PC-3M cells and NIH3T3 (mouse fibroblast) cells in the sub-G1 stage and thus induced apoptosis of these cell lines [54].

2.3.2. Naphthoquinones

Bikaverin **48** was a quinone metabolite first obtained as an antibiotic from mycelium of *Gibberella fujikuroi* [55]. Zhan and coworkers also isolated it from the fungal strain *Fusarium oxysporum* EPH2RAA in *Ephedra fasciculate*. It showed selective cytoxicity towards NCI-H460, MIA PaCa-2, MCF-7 and SF-268 with IC_{50} values of 0.43, 0.26, 0.42 and 0.38 μM, respectively [56]. Isodiospyrol A **49** was a fungal metabolite in fruits of *Diospyros ehretioides* and exhibited cytotoxic activities towards BC cell line (IC_{50} 12.3 μg/mL) [57].





45 torreyanic acid

46 (+)-epiepoxydon

47 tauranin

48 bikaverin

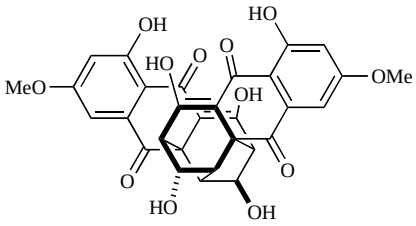
49 isodiospyrol A

2.3.3. Anthraquinones

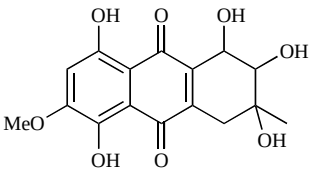
A rare bisanthraquinone cytoskyrin A **50** was isolated from *Cytospora* sp. in *Conocarpus erecta*. It exhibited potent DNA-damaging activities (10 ng/spot) and inhibited to four human carcinoma cell lines including DA-MB-435 (breast carcinoma), A431 (epidermoid carcinoma), SW620 (colon carcinoma) and SKBR3 (breast carcinoma) with IC_{50} values range from 3.6 to 24.3 μg/mL [58-59]. In addition, SZ-685C **51** was an anthraquinone from the fungus No. 1403 and it suppressed the proliferation of six tumor cell lines derived from human breast cancer, prostate cancer, glioma and hepatoma with IC_{50} values ranged from 3.0 to 9.6 μM. *In vivo* anti-tumour efficacy was examined in an MDA-MB-435 breast cancer xenograft model. The result indicated a intraperitoneal dosage of 50mg/kg SZ-685C every 3 days exhibited a 61% inhibition of tumour growth. Underlying molecular mechanisms showed SZ-685C had a direct apoptosis-inducing effect by activation of caspase-8 and 9 both the extrinsic and intrinsic apoptotic pathways, and affected orcaspase-3 and poly (ADP-ribose) polymerase. SZ-685C could also induce apoptosis through the Akt/FOXO pathway, which consequently leads to the observed antitumour effect both *in vitro* and *in vivo*. Thus SZ-685C may be a potentially anticancer drug candidate [60].

More recently, five anthracenedione derivatives **52-56** with cytotoxicity against KB and KBv200 cells were separated from the mangrove endophytic fungi *Halorosellinia* sp. and *Guignardia* sp. [61]. Among which compound **54** displayed stronger cytotoxicity with IC_{50} values of 3.17 and 3.21 μM, respectively. The mechanism involved in the apoptosis induced by compound **54** was related to mitochondrial dysfunction, including loss of mitochondrial potential [62]. Ge and coworkers isolated a new hexahydroanthraquinone named pleospdione **57** together with 7-methoxy-2-methyl-3, 4, 5-trihydroxy-anthraquinone **58**, physcion **59**, deoxybostrycin **60**, altersolanol B **61** and dactylariol **62** from *Pleospora* sp. IFB-E006 in *Imperata cylindrical*. Compounds **60-62** exhibited significant cytotoxicity towards SW1116 and K562 tumor cell lines while compounds **57-59** were only weakly or moderately active [63]. 3-*O*-Methylalaternin **63** and altersolanol A **64** were two anthraquinones exhibited in fungal endophyte *Ampelomyces* sp. in a medicinal plant *Urospermum picroides* and showed strong cytotoxic activity against L5178Y (mouse lymphoma cells) with EC_{50} values of 1.25 and 0.21 μg/mL, respectively [64]. From the cultures of *Thielavia subthermophila* growing in *Hypericum perforatum*, two metabolites hypericin **65** and emodin **66** were purified. Biological assays indicated that they exhibited photodynamic cytotoxicity against THP-1 (human acute monocytic leukemia cell line) [65].

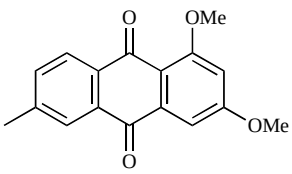
More recently, Debbab and coworkers isolated a series of anthraquinones including mixtures of alterporriols A-B **67-68**, D-E **69-70**, G-H **71-72** and altersolanols A, J, K, L **73-76** together with 6-*O*-methylalaternin **77**, macrosporin **78** from the endophytic fungus *Stemphylium globuliferum* in the Moroccan medicinal plant *Mentha pulegium*. All the compounds showed cytotoxicity against L5178Y cells, among which the mixture of alterporriols G **71** and H **72** exhibited considerable effect with an EC_{50} value of 2.27 μg/mL. The compounds were also tested for kinase inhibitory activity involving 24 different kinases which



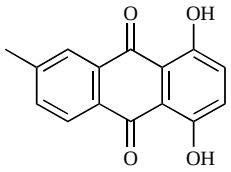
50 cytoskyrin A



51 SZ-685C



52



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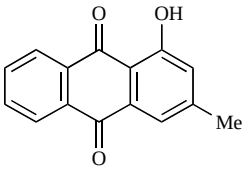

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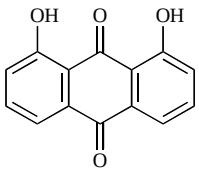

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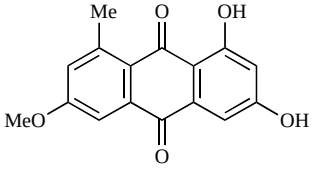
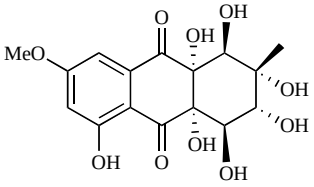
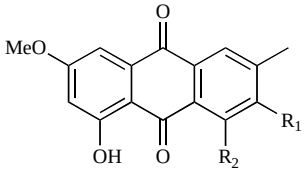


56

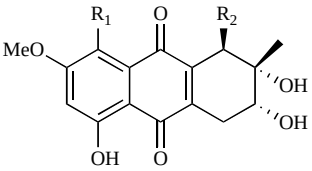


57 pleospdione



58 $R_1 = R_2 = OH$

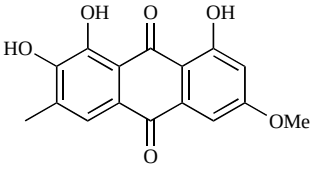
59 physcion, $R_1 = H$, $R_2 = OH$



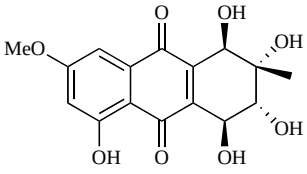
60 deoxybostrycin, $R_1 = OH$, $R_2 = H$

61 altersolanol B, $R_1 = R_2 = H$

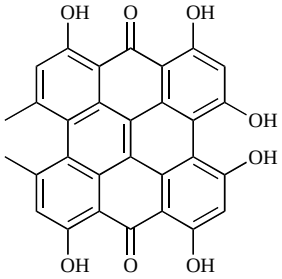
62 dactylariol, $R_1 = H$, $R_2 = OH$



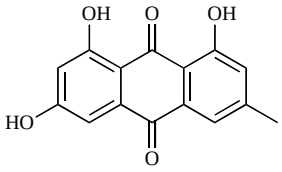
63 3-*O*-methylalaternin



64 altersolanol A



65 hypericin



66 emodin

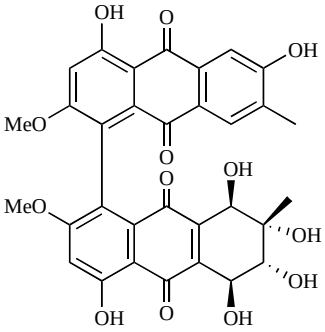
might be one of the major mechanisms contributing to the toxic effect and the mixture of **71-72** and compounds **73, 77-78** were the most potent inhibitors [66].

2.4. Flavonoids

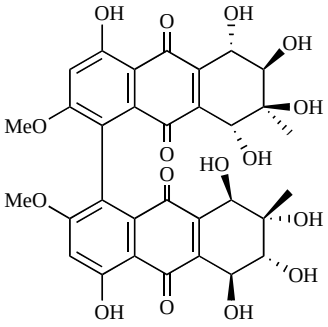
Flavonoids are a class of polyphenolic compounds widely distributed in the plant kingdom and their endophytes. Flavonoid family is a good reservoir for potential anticancer agents. The flavonoids with antitumor activities from endophytic fungi are mainly xanthones and chromones.

2.4.1. Xanthones

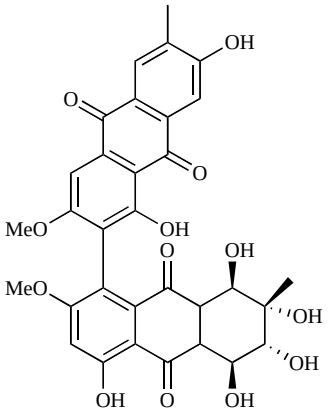
Xanthone derivatives are widespread in nature, commonly occurring in a number of higher plant families and fungi [67]. The antitumor xanthones in endophyte were monomers, dimmers or metabolites derived from xanthons. Dicerandrols A, B and C (**79-81**) were three xanthone dimmers exhibited in culture of *Phomopsis longicolla* in the endangered mint *Dicerandra frutescens*. All these compounds possessed strong activity against two human cancer cell lines, A549 (human lung carcinoma, IC_{100} 7.0, 1.8, 1.8 μg/mL) and HCT-116 (IC_{100} 7.0, 1.8, 7.0 μg/mL) [68]. Isaka and coworkers purified two novel flavonoids, phomoxanthones A **82** and B **83** from the teak endophyte *Phomopsis* sp. BCC1323 collected from northern Thailand, and the two compounds exhibited significant cytoxic activity towards KB (IC_{50} 0.99, 4.1μg/mL) and BC-1 (IC_{50} 0.51, 0.70 μg/mL) cell lines [69]. The dimeric xanthene ergoflavin **84** was purified from an endophytic fungus of the Ascomycetes



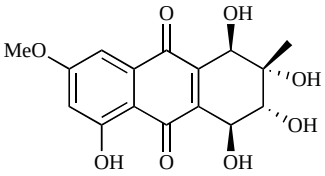
67, 68 alterporriols A-B (atropisomers)



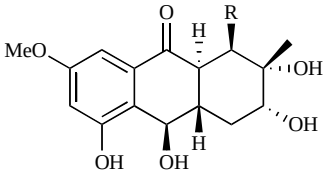
69, 70 alterporriols D-E (atropisomers)



71, 72 alterporriols G-H (atropisomers)

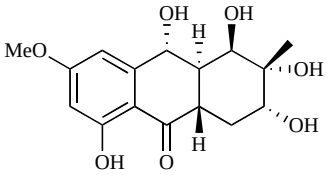


73 altersolanol A

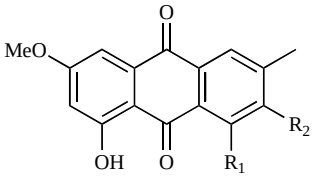


74 altersolanol J, R = H

75 altersolanol K, R = OH



76 altersolanol L



77 6-*O*-methylalaternin, $R_1 = R_2 = OH$

78 macrosporin, $R_1 = H$, $R_2 = OH$

family growing on an Indian plant *Mimosops elengi* and exhibited significant inhibition of ACHN (human renal cell carcinoma), H460, Panc1, HCT116, and Calu1 cancer cell lines [70].

A new dihydroxanthenone named globosuxanthone A **85** was elaborated by fungal strains *Chaetomium globosum* in *Opuntia leptocaulis* [71] and endophyte *Microdiplodia* sp., respectively [72]. It was found to exhibit strong cytotoxicity against a panel of seven human solid tumor cell lines including NCI-H460, MCF-7, SF-268, PC-3 (hormone independent prostate adenocarcinoma) , PC-3M, LNCaP and DU-145 (hormone-independent prostate cancer). Further study indicated the compound disrupted the cell cycle leading to the accumulation of cells in either G2/M or S phase, and induced classic signs of apoptosis [71]. 1,7-Dihydroxy-methoxy-3-(3-methylbut-2-enyl)-9H-xanthen-9-one **86** and 1-hydroxy-4,7-dimethoxy-6-(3-oxobutyl)-9H-xanthen-9-one **87** were isolated from a mangrove endophytic fungus (No.ZH19) in the South China Sea. The two compounds inhibited KB cells with IC_{50} values of 20 and 35 μM, and KBV200 cells with IC_{50} values of 30 and 41 μM, respectively [67].

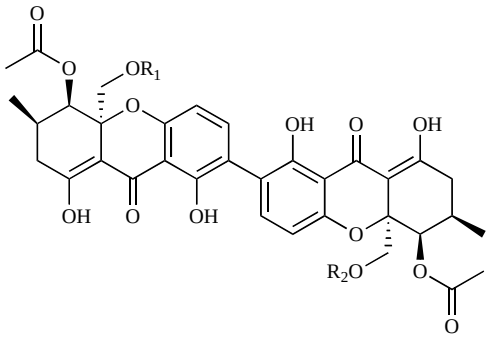
2.4.2. Chromones

Pestalotiopsone F **88** was a chromone purified from *Pestalotiopsis* sp. colonising the Chinese mangrove plant *Rhizophora mucronata* and showed moderate cytotoxicity to the murine cancer cell line L5178Y [73].

2.5. Isocoumarins and Lignans

2.5.1. Isocoumarins

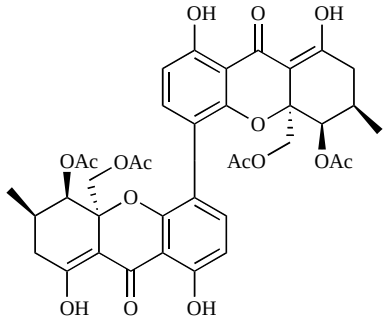
Up to now, only two novel isocoumarin derivatives have been separated from endophytic sources with antitumor activity. 3, 4-Dihydro-6-methoxy-8-hydroxy-3, 4, 5-trimethylisocoumarin-7-carboxylic acid methyl ester **89** was purified from marine-derived mangrove endophytic fungus (No. dz17) in the South China Sea. Primary bioassays showed that **89** exhibited weak inhibition of Hep-2 and HepG2 cells [74]. Desmethyldiaportinol **90** was obtained together with two antitumor quinones altersolanol A **73** and 6-*O*-methylalaternin **77** from the endophytic fungus *Stemphylium globuliferum* described above, and it also showed siginificant cytotoxic activity against L5178Ycells with EC_{50} of 7.30 μg/mL [64].



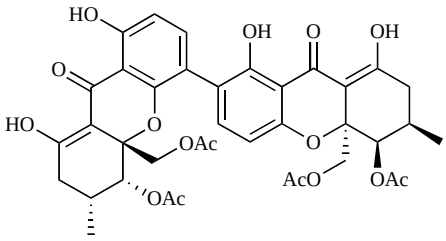
79 dicerandrol A, $R_1 = R_2 = H$

80 dicerandrol B, R_1 =Ac, $R_2 = H$

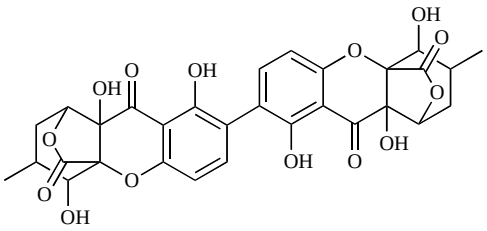
81 dicerandrol C, R1 = R2 = Ac



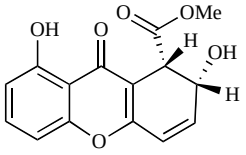
82 phomoxanthone A



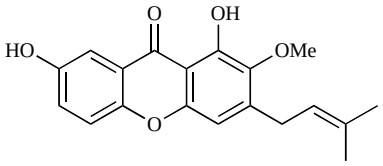
83 phomoxanthone B



84 ergoflavin



85 globosuxanthone A



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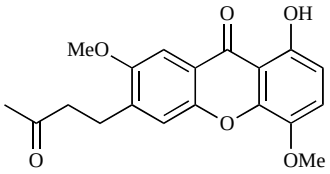

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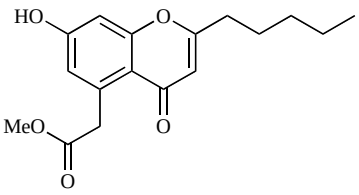
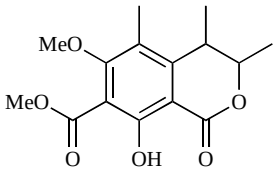


88 pestalotiopsone F



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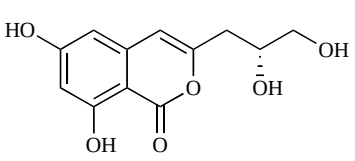
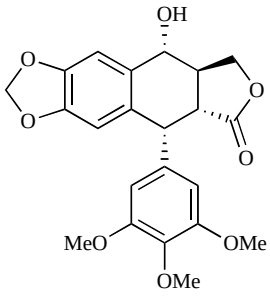
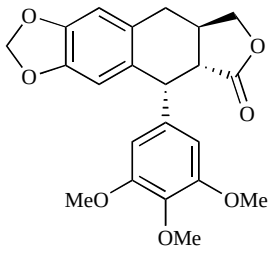


90 desmethyldiaportinol



91 podophyllotoxin



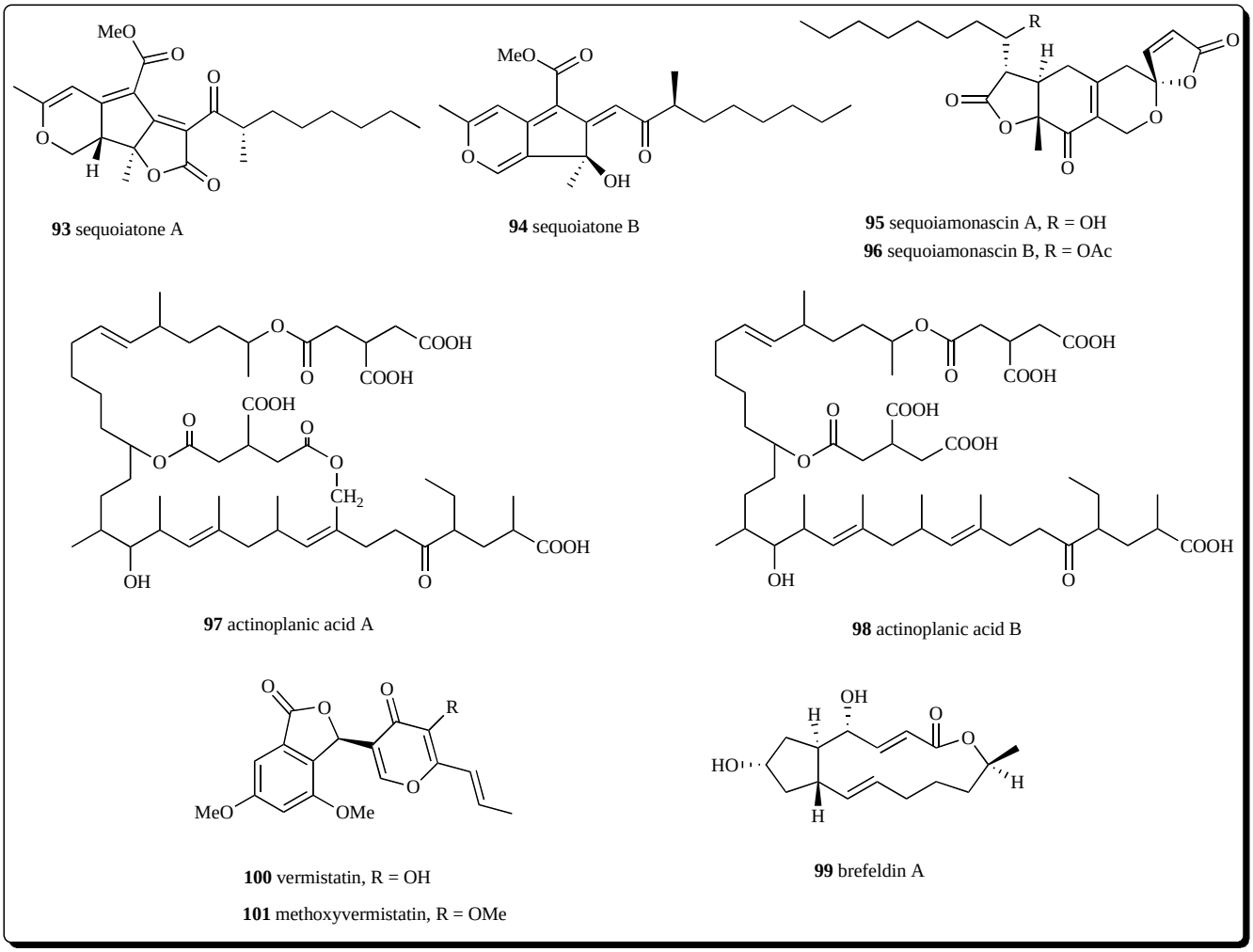
92 deoxypodophyllotoxin (DPT)

2.5.2. Lignans

The lignan podophyllotoxin **91** is highly valued precursor of clinically useful antitumor drugs. It inhibits the catalytic activity of DNA topoisomerase II by stabilizing a cleavage enzyme-DNA complex in which the DNA is cleaved and covalently linked to the enzyme [75]. Eyberger and coworkers [76] obtained podophyllotoxin in two endophytic fungi, both strains of *Phialocephala fortinii*, from rhizomes of the medicinal plant *Podophyllum peltatum*. Its pro-drug Deoxypodophyllotoxin (DPT, **92)** was shown to demonstrate remarkable antitumor activities against a number of tumor cell lines including A549, SK-OV-3, SK-MEL-2, HCT15 and B16F10 with ED_{50} value ranged from 6 to 18 ng/mL. Furthermore, a intraperitoneal daily dosage of 20 mg/kg DPT for 14 days exhibited an inhibition ratio of 60 % on BDF1 mice bearing Lewis lung carcinoma cells [77]. Kusari and coworkers isolated DPT from the endophytic *Aspergillus fumigatus* colonising *Juniperus communis* [78].

2.6. Lactones and Esters

Lactones and esters are extensively distributed in plants with many important physiological effects, and interestingly a lot of lactones and esters with antitumor activity from endophytic fungi have been reported. Two lactones sequoiatones A **93** and B **94** were isolated from *Aspergillus parasiticus* residing in *Sequoia sempervirens* [79]. Primary antitumor testing showed that they had moderate and somewhat selective inhibition of human tumor cells *in vitro*, with greatest efficacy against breast cancer cell lines. Additionally, two novel lactones, sequoiamonascins A-B (**95-96**) [80] were also purified from *A. parasiticus*. Both compounds showed selective cytotoxic activity towards three cancer cell lines, MCF7, NCI-H460 and SF-268. Metabolites actinoplanic acids A **97** and B **98** were potent inhibitors of Ras Farnesyl-Protein Transferase (FPTase) produced by fermentation of *Actinoplanes* sp., an endophyte in lichen on oak tree [81]. Brefeldin A **99** was a microbial-specific metabolite produced by a number of fungi which belonging to the genera *Alternaria*, *Ascochyta*, *Penicillium*, *Curvularia*, *Cercospora*, *Phyllosticta* and *Paecilomyces*. It was also obtained from endophytic *Paecilomyces* sp. and *Aspergillus clavatus* isolated from *Taxus mairei* and *Torreya grandis* [82]. Brefeldin A showed high inhibition of HL-60, KB, Hela, MCF-7, Spc-A-1 BC-1 and NCI-H187 cell lines (IC_{50} range from 1.0 to 10.0 ng/mL). Cytotoxicities against Hela, MCF-7 and Spc-A-1 tumor cell lines were close to that of taxol. brefeldin A is therefore a very promising compound in the area of cancer therapy [15, 83]. The differentiation-inducing activity of Brefeldin A to cancer cells was due to its modulatory effect on ganglioside biosynthesis, and that a



93 sequoiatone A

94 sequoiatone B

95 sequoiamonascin A, R = OH

96 sequoiamonascin B, R = OAc

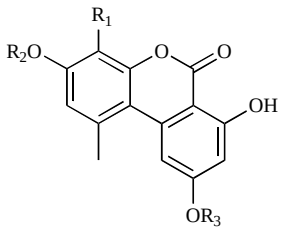
97 actinoplanic acid A

98 actinoplanic acid B

100 vermistatin, R = OH

101 methoxyvermistatin, R = OMe

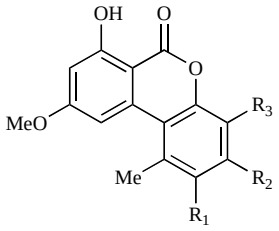
99 brefeldin A



102 alternariol, $R_1 = R_2 = R_3 = H$

103 alternariol 5-*O*-sulfate, $R_1 = R_2 = H$, $R_3 = SO_3H$

104 alternariol 5-*O*-methylether, $R_1 = R_2 = H$, $R_3 = CH_3$

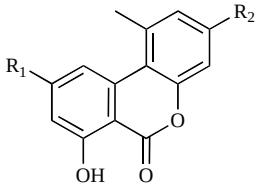


105 graphislactone G, $R_1 = Cl$, $R_2 = MeO$, $R_3 = H$

106 graphislactone H, $R_1 = H$, $R_2 = R_3 = MeO$

107 graphislactone A, $R_1 = H$, $R_2 = MeO$, $R_3 = OH$

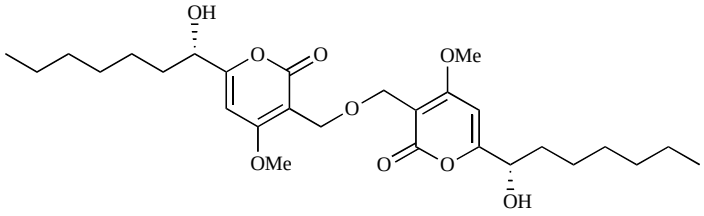
108 alternariol monomethylether, $R_1 = H$, $R_2 = OH$, $R_3 = H$



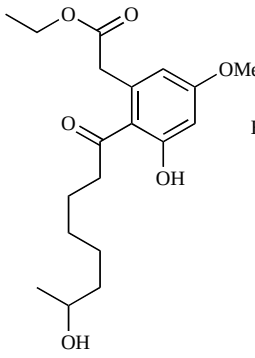
109 2240B, $R_1 = OMe$, $R_2 = Ac$

110 $R_1 = R_2 = OMe$

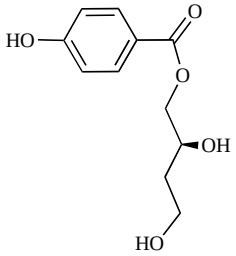
111 $R_1 = OMe$, $R_2 = OH$



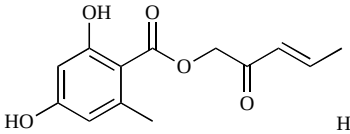
112 dothideopyrone D



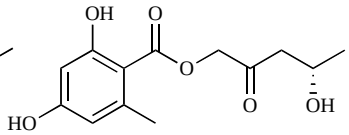
113



114



115 globosumone A



116 globosumone B

specific change in ganglioside pattern is an essential prerequisite for induction of differentiation which is a target for differentiation therapy of cancer [83]. Two new vermistatin derivatives, vermistatin **100** and methoxy-vermistatin **101** were isolated from the marine endophytic fungus *Guignardia* sp. obtained from the South China Sea [84]. Bioactivity tests indicated that compound **101** exhibits modest toxic activity against KB and KBv200 cells *in vitro*, with IC_{50} values of 20.0 and 15.1 μg/mL, respectively. For comparison, vermistatin **100** inhibited the KB tumor cell line with an IC_{50} value of 90.2 μg/mL.

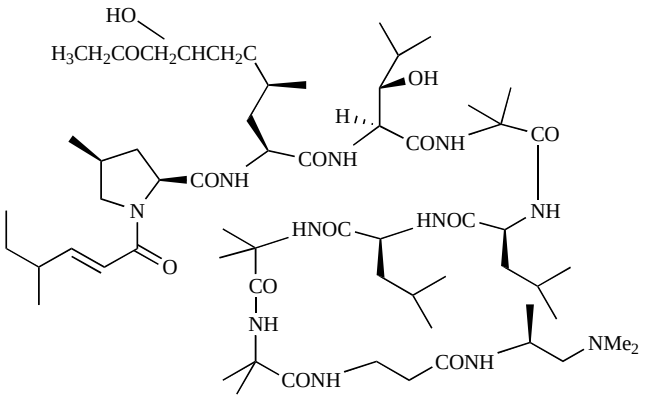
Three polyketide metabolites alternariol **102,** alternariol 5-*O*-sulfate **103** and alternariol 5-*O*-methylether **104** were purified from *Alternaria* sp. in the Egyptian medicinal plant *Polygonum senegalense.* All these compounds showed toxicity towards L5178Y mouse lymphoma cells with EC_{50} values of 1.7, 4.5 and 7.8 μg/mL, respectively [85]. Two novel alternariol derivatives, graphislactone G **105**, graphislactone H **106** together with graphislactone A **107**, alternariol monomethylether **108** were metabolites from medicinal plant *Cephalosporium acremonium* IFB-E007 in *Trachelospermum jasminoides*. All the compounds had pronounced activities against SW1116 cell (human colorectal carcinoma) with IC_{50} values of 21, 12, 8.5 and 14 μg/mL, respectively [86].

The research group of Tan [87] isolated four alternariol derivatives including 2240B **109,** alternariol **102**, alternariol 4, 10-dimethyl ether **110** and alternariol 4-methyl ether **111** **f**rom mangrove endophytic fungus in the South China Sea Coast. The antitumor tests showed that compounds **102** and **111** had strong activities against KB and KBv200 cells with IC_{50} values of 3.17, 3.12, 4.82 and 4.94 μg/mL, respectively. While compounds **109-110** exhibited weak activities against these tumor cell lines with IC_{50} values of more than 50

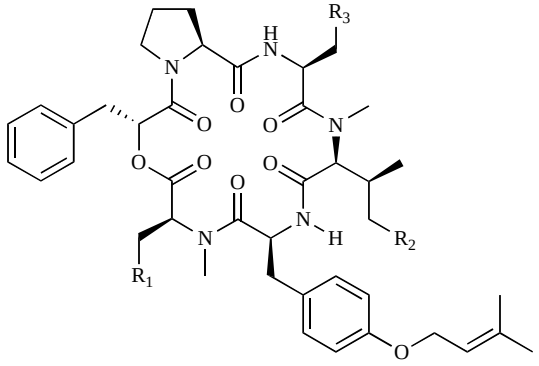
μg/mL. A pyrone derivative dothideopyrone D **112** was purified from the endophytic mitosporic Dothideomycete sp. LRUB20 in a Thailand medicinal plant, *Leea rubra*. It exhibited moderate inhibitory activity against nine cancer cell lines [88]. A new polyketide, 2-(7'-hydroxyoxooctyl)-3-hydroxy- 5-methoxy-benzeneacetic acid ethyl ester **113** was separated from the endophytic fungus *Phomopsis* sp. ZSU-H76 in mangrove tree *Excoecaria agallocha* from Dong Zai, Hainan, China. Primary bioassays showed that it could inhibit the growth of HEp-2 and HepG2 cells with IC_{50} values of 25 and 30 μg/mL, respectively [89]. Additionally, (S)-2, 4-dihydroxy-1-bu (4-hydroxy) benzoate **114** was also purified from *Penicillium auratiogriseum* and showed toxic activity against tsFT210 cancer cells with maximum inhibitory effect observed at 8.0 μg/mL [30]. Globosumones A-B (**115-116**) were orsellinic acid esters purified from *Chaetomium globosum* endophytic on *Ephedra fasciculata* (Mormon tea) and exhibited moderately active against four cancer cell lines including NCI-H460, MCF-7, SF-268(CNS glioma) and MIA Pa Ca-2 [90].

2.7. Peptides

Leucinostatin A **117** was a peptide previously obtained from *Penicillium lilacinum* and *Paecilomyces lilacinus* [91-92]. It was also separated from *Acremonium* sp. endophytic in European yew. It possessed strong activity against a panel of 21 human cancer cell lines [93]. Pullularins A–C **118-120** were cyclohexadepsipeptides purified from the endophytic



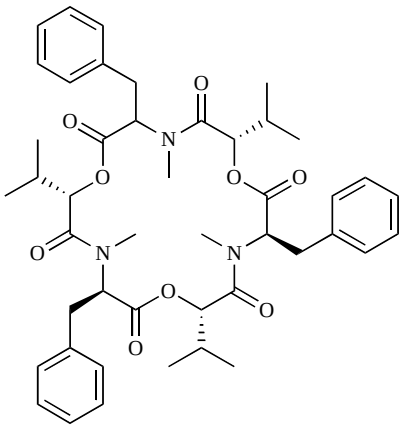
117 leucinostatin A



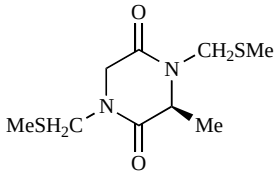
118 pullularin A, R_1 = H, R_2 = CH_3, R_3 = OH

119 pullularin B, R_1 = R_2= CH_3, R_3 = OH

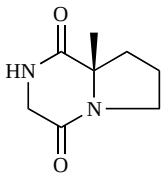
120 pullularin C, R_1 = R_2 = H, R_3 = OH



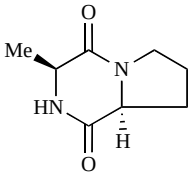
121 beauvericin



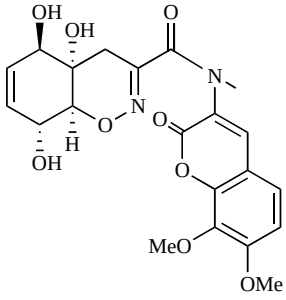
122 cyclo-(Ala-Gly)



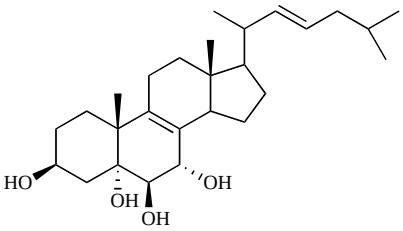
123 cyclo-(Pro- Gly)



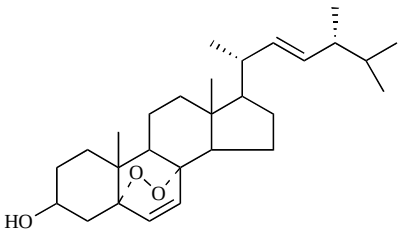
124 cyclo-(Ala-Pro)



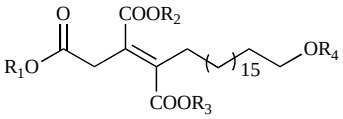
125 trichodermamide C



126

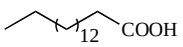


127

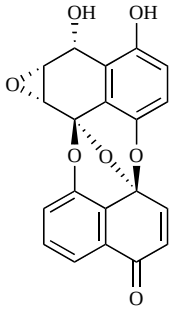


128 oreganic acid $R_1 = R_2 = R_3 = H$, $R_4 = SO_3H$

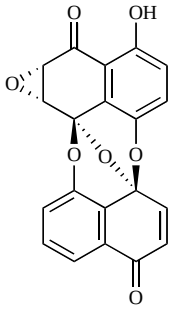
129 $R_1 = R_2 = R_3 = R_4 = H$



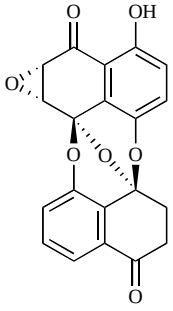
130 palmtic acid



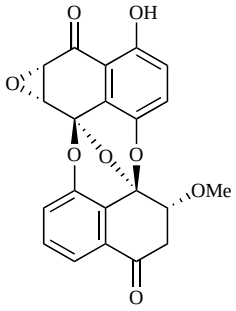
131 preussomerin D



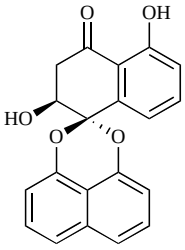
132 preussomerin G



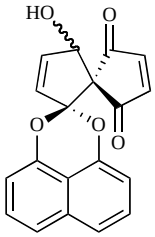
133 preussomerin H



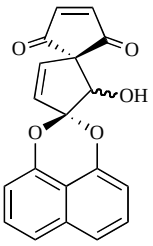
134 preussomerin I



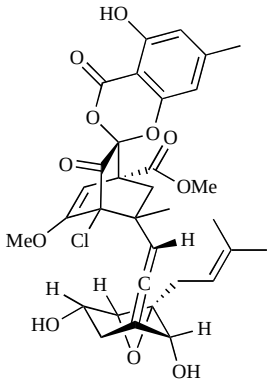
135 palmarumycin JC2



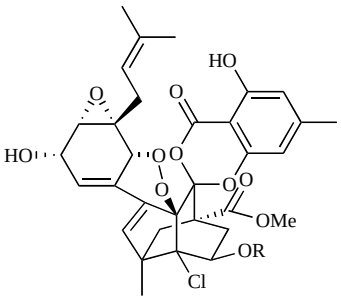
136 *spiro*-mamakone A



137 spiropreussione A

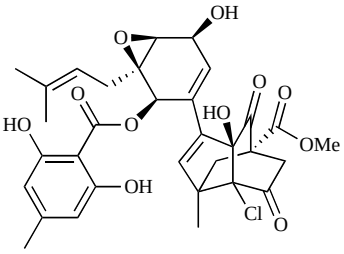


138 chloropestolide A



139 chloropupukeanolide A, R = CH_3

140 chloropupukeanolide B, R = H



141 chloropupukeanone A

fungus *Pullularia* sp. BCC8613 in *Culophyllum* sp. All these compounds exhibited modest cytotoxic activity against KB, BC, NCI-H187 cell lines [94]. Beauvericin **121** was a depsipeptide first encountered in *Beauveria bassiana* [95]. It was obtained together with bikaverin in *Fusarium oxysporum* occurring in *Cylindropuntia echinocarpus* [56]. Beauvericin showed selective toxicity towards NCI-H460 and MIA Pa Ca-2, respectively. It induced apoptosis through multiple cellular molecular pathways including pro- and antiapoptotic Bcl-2 family proteins, mitochondrial membrane potential, mitochondrial cytochrome *c* and caspase 3 [96].

Three cyclodipeptide cyclo-(Ala-Gly) **122**, cyclo-(Pro-Gly) **123**, cyclo-(Ala-Pro) **124** from *Penicillium thomi* were found to have cytotoxicity against three human cancer cell lines A549, HepG2, HT29 (colorectal carcinoma cell) and gave IC_{50} values in the range 8.9-20.1 μM [97]. Davis and coworkers [98] isolated a modified dipeptide tricho-dermamide C **125** in endophytic fungus *Eupenicillium* sp. in the rain forest tree *Glochidion ferdinandi*. Compound **125** displayed toxicity towards the human colorectal carcinoma HCT116 and human lung carcinoma A549 with IC_{50} values of 0.68 and 4.28 μg/mL, respectively.

2.8. Miscellaneous Metabolites

In addition to various types of natural products from fungal endophyte which have been described in the above, there are still other endophytic metabolites including steroids, aliphatic compounds, spirobisnaphthalenes etc. A novel sterol, ergosta-8(9), 22-diene-3, 5, 6, 7-tetraol (3β, 5α, 6β, 7α, 22E) **126** was isolated from the mycelia of an unidentified endophytic fungus in *Castaniopsis fissa*. Compound **126** exhibited potent selective inhibition of Bel-7402, NCI-4460 and L-02 cell lines with IC_{50} values of 8.445, 5.03 and 13.621 μg/mL, respectively [99]. 3β-Hydroxy-5α, 8α-epidioxy-ergosta-6, 22-diene **127** was a steroid widely distributed in fungi and lichens. It showed potent cytotoxity against mouse lymphaemiaL-1210/v/c strain (LD_{50} 11.7 μg/mL) and KB cell (LD_{50} 12.3 μg/mL) [100-101].

Up to now, only three aliphatic compounds with antitumor activity have been obtained from fungal endophytes. Oreganic acid **128** and its desulfated analogue **129** from a fungal endophyte in *Berberis oregana* were two potent and highly specific inhibitors of FPTase with IC_{50} values of 14 nM and 3.3 μM, respectively [102-103]. Chen and coworkers [104] isolated palmtic acid **130** from the endophytic fungus S26 of *Cephalotaxus hainanensis*. It had moderate inhibition of gastric cancer cell SGC-7901.

Spirobisnaphthalenes are a relatively new class of compounds involving two or three oxygen atoms acting as bridges connecting two original naphthalene subunits. Preussomerin D **131** [105], preussomerin G-I (**132-134**) [106], Palmarumycin JC2 **(135)** [57], *spiro*-mamakone A **136** [107] and spiropreussione A **137** [108] were a series of spirobisnaphthalenes with antitumor activity obtained from fungal endophyte. Their structural characters and biological activities as well as their structure-activity relationship, mechanism of action have already reported in recent review article [109].

Liu and coworkers purified a series of antitumor metabolites with unprecedented spiroketal peroxides from *Pestalotiopsis fici* which were identified as chloropestolide A **138** [110], chloropupukeanolides A **139**, B **140** and chloropupukeanone A **141** [111]. Among which compound **138** showed significant inhibitory effects on growth of human cancer cell lines, HeLa, HT29, while compounds **139-141** had moderate cytotoxicity against HeLa, MCF-7, MDA -MB-231 cancer cells.

3. CONCLUSIONS

Fungal endophytes are a poorly investigated group of microorganisms that represent an abundant and dependable natural resource of novel bioactive products with great potential for further exploitation. It requires specific rationales and imaginative strategies to find antitumor compounds in endophytic fungi. Plant selection rationales include selecting plants from unique environmental settings or those growing in areas of great biodiversity, such as tropical mangrove swamps, and investigating traditional anticancer pharmaceutical plants, such as *T. brevifolia*, *Camptotheca acuminate*, and *Podophyllum peltatum* etc. These selection criteria provide the main plant sources for current and future investigations of antitumor metabolite-producing endophytes. An important strategy for isolating plant endophytes and natural products with antitumor activity is bioassay-guided screening and separation based on cancer-specific mechanisms and corresponding molecular targets. Microtubule inhibitors (e.g., taxol), intranuclear enzyme topoisomerase I inhibitors (e.g., camptothecin), topoisomerase II inhibitors (e.g., podophyllotoxin) as well as inhibitors of farnesyl-protein transferase (e.g., TAN-1813) which have been described in this article, offer attractive and promising approaches as anticancer agents.

Fungal endophytes, with their biodiversity, chemical diversity and metabolites with unique biological activity, are a promising resource for further discoveries in both chemical and biological sciences and have the potential to provide therapeutic agents for many diseases, including cancer.

ACKNOWLEDGEMENTS

This work was supported by National Natural Science Foundation of China (Grant No. 30600002 and No.30970097) to Chu-long Zhang and Young Engagement Foundation of Hangzhou Normal University (No. 2010QN21) to Li-wei Wang.

ABBREVIATIONS

A549	=	human lung carcinoma
ACHN	=	human renal cell carcinoma
BC-1	=	Human breast cancer
BEL-7404	=	human liver carcinoma cell
B16F10	=	melanoma
CHO	=	Chinese hamster ovary
CPT	=	Camptothecin

DU-145 = hormone-independent prostate cancer

ED_{50} = half maximal effective concentration

FPTase = Inhibitors of farnesyl-protein transferase

GI_{50} = Concentration that causes 50% cell growth inhibition

HCT-116 = colon tumor cell line

HeLa = human cervix carcinoma

HT29 = colorectal carcinoma cell

HCT116 = human colorectal carcinoma

IC_{50} = 50% Cytotoxic concentration

KB = Human epidermoid carcinoma of the mouth

KV/MDR = human oral floor carcinoma cells

K562 = leukemia

LD_{50} = median lethal dose

LNCaP = human chronic myelogenous leukemia

LOVO = human colon adenocarcinoma

L1210 = leukemia cells

L5178Y = mouse lymphoma cells

MCF-7 = breast cancer cells

MIA Pa Ca-2 = pancreatic cancer cells

NCI-H187 = Human small cell lung cancer

NCI-H460 = non small cell lung

NIH 3T3 = mouse fibroblast

NIH3T3/K-*ras* = K-*ras* transformant of mouse embryonic fibroblast cell line

OAc = acetate

OMe = Methoxy

SW-620 = colon tumor cell line

2780S = ovarian tumor cell line

PC-3M = prostate tumor cell line

PC-3 = hormone- (androgen) independent prostate adenocarcinoma

SF-268 = CNS glioma

STAT3 = the signal transducer and activator of transcription 3

SW1116 = human colorectal carcinoma

THP-1 = human acute monocytic leukemia cell line

tsFT210 = the mouse cdc2 mutant cell

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Received: March 03, 2011 Revised: May 18, 2011 Accepted: June 06, 2011