CHAPTER II

LITERATURE REVIEW

An increase in the number of people in the world having health problems has been caused by various diseases, especially cancers. Discovering new compounds from natural products is very important for formulating new drugs. Endophytic fungi have been recognized as a new source for pharmaceutically important compounds that can be used in the treatment of various life threatening diseases. (Strobel 2002).

1. Endophytic Fungi

Endophytic fungi are symbiotic microorganisms living within tissues of the plant hosts without causing noticeable diseases. At times, endophytic fungi are known to prevent the host plants from successfully attacking other organisms and improve the resistance of the host plants by producing the bioactive secondary metabolites (Strobel and Daisy 2003). In addition, these endophytic fungi have been widely investigated for diverse bioactive secondary metabolites exhibiting a variety of biological activities against different diseases. Interestingly, some endophytic fungi have been reported to produce bioactive compounds previously isolated from their host plants (Joseph and Priya 2011).

2. Anticancer Agents from Endophytic Fungi

Endophytic fungi have been studied as a source of anticancer agents since the isolation of taxol **[1]** from the endophytic fungus *Taxomyces andreanae*. Taxol was isolated for the first time from the bark of Pacific yew tree, *Taxus brevifolia*. Nevertheless, the trees are rare, slow growing and produce small amount of taxol, implying its high price in the market. Furthermore, the use of plant source as the unique option has limited the supply of this drug. The isolation of taxol-producing endophytic fungus *Taxomyces andreanae* has provided an alternative approach to gain more amounts of taxol by fungal fermentation (Stierle *et al.,* 1993).

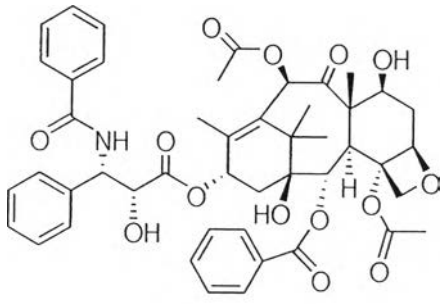
The anticancer agents from endophytic fungi and host plants are summarized in **Table 1**, and their chemical structures are shown in **Figure 1**.

Table 1. Anticancer agents from endophytic fungi.

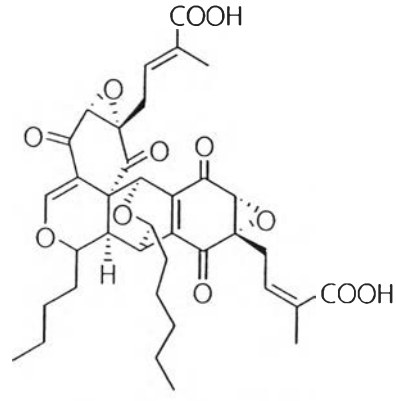
Compound	Endophytic fungus	Host plant	Reference
Taxol [1]	*Taxomyces andreanae*	*Taxus brevifolia*	(Stierle *et al.*, 1993)
Torreyanic acid [2]	*Pestalotiopsis microspora*	*Torreya taxifolia*	(Lee *et al.*, 1996)
Sequoiatone A [3]	*Aspergillus parasiticus*	*Sequoia sempervirens*	(Stierle *et al.*, 1999)
Rubrofusarin B [4]	*Aspergillus niger* IFB-E003	*Cynodon dactylon*	(Song *et al.*, 2004)
Camptothecin [5]	*Entrophospora infrequens*	*Nothapodytes foetida*	(Puri *et al.*, 2005)
	Fusarium solani	*Camptotheca acuminata*	(Kusari *et al.*, 2009)
Periconicin B [6]	*Periconia atropurpurea*	*Xylopia aromatic*	(Teles *et al.*, 2006)
Podophyllotoxin [7]	*Trametes hirsuta*	*Podophyllum hexandrum*	(Puri *et al.*, 2006)
Radicicol [8]	*Chaetomium chiversii*	*Ephredra fasciculata*	(Turbyville *et al.*, 2006)
Beauvericin [9]	*Fusarium oxysporum* $EPH2R_{AA}$	*Ephedra fasciculata*	(Zhan *et al.*, 2007)
Bikaverin [10]	*Fusarium oxysporum* CECIS	*Cylindropuntia echinocarpus*	

Table 1. (continued)

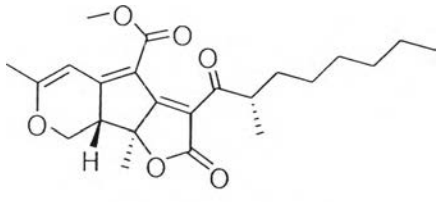
Compound	Endophytic fungus	Host plant	Reference
Daldinones C-D **[11-12]**	*Hypoxylon truncatum* IFB-18	*Artemisia annua*	(Gu *et al.*, 2007)
Alternariol **[13]**	*Alternaria* sp.	*Polygonum senegalense*	(Aly *et al.*, 2008)
Tauranin **[14]**	*Phyllosticta spinarun*	*Platycladus orientalis*	(Wijeratne *et al.*, 2008)
Cochliodinol **[15]**	*Chaetomium* sp.	*Salvia officinalis*	(Debbab *et al.*, 2009)
Eutypellin A **[16]**	*Eutypella* sp. BCC 13199	*Etlingera littoralis*	(Isaka *et al.*, 2009)
Sclerotiorin **[17]**	*Cephalotheca faveolata*	*Eugenia jumbolana*	(Giridharan *et al.*, 2012)



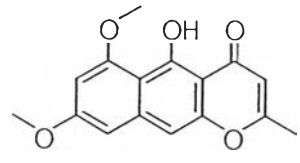
Taxol [1]



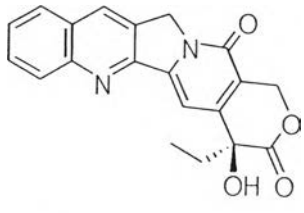
Torreyanic acid [2]



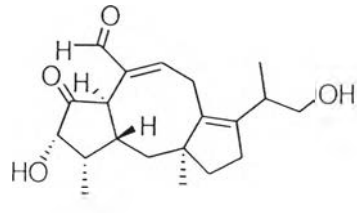
Sequoiatone A [3]



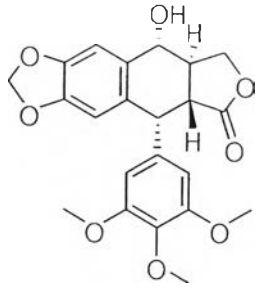
Rubrofusarin B [4]



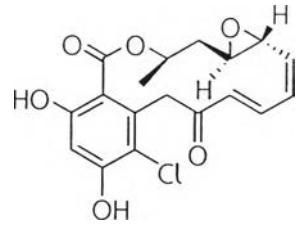
Camptothecin [5]



Periconicin B [6]

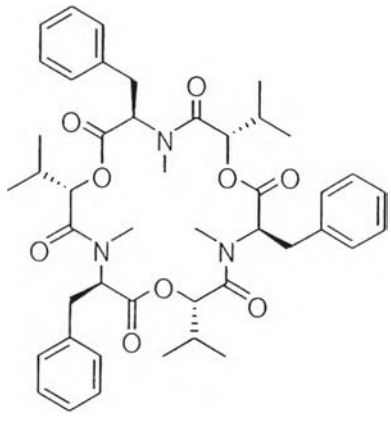


Podophyllotoxin [7]

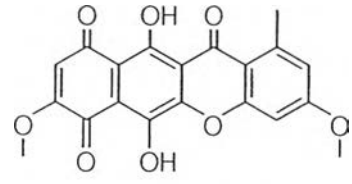


Radicicol [8]

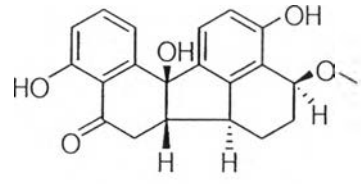
Figure 1. Anticancer agents from endophytic fungi.



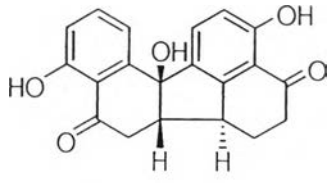
Beauvericin [9]



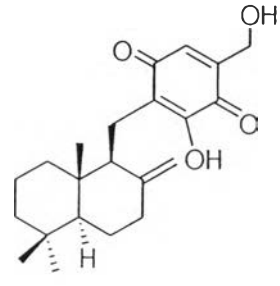
Bikaverin [10]



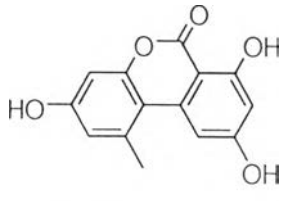
Daldinone D [12]



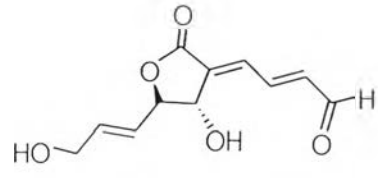
Daldinone C [11]



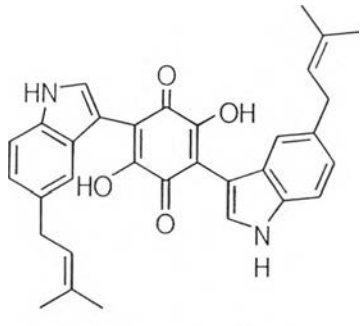
Tauranin [14]



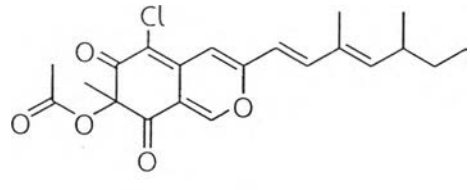
Alternariol [13]



Eutypellin A [16]



Cochliodinol [15]



Sclerotiorin [17]

Figure 1. (continued)

3. Antileukemic Agents from Endophytic Fungi

The screening of 172 endophytic fungi isolated from Chinese medicinal plants showed 13.4 % of endophytes produced antileukemic substances on HL-60 cell line (Huang *et al.*, 2001). This evidence suggested that endophytic fungi could be an alternative source for discovery of novel antileukemic agents.

The antileukemic constituents found in endophytic fungi together with host plants, cell lines and EC_{50} are summarized in **Table 2**, and their chemical structures are shown in **Figure 2**.

4. Anticancer Agents from *Phomopsis*

The endophytic fungi in the genus *Phomopsis* belonging to Diaporthaceae family have been reported as the endophytes in several plants and marine organisms. The *Phomopsis* endophytes have been found to be a source of biologically active secondary metabolites, particularly anticancer activity.

The anticancer agents found in the endophytic fungus *Phomopsis* together with host plants and cell lines are summarized in **Table 3**, and their chemical structures are shown in **Figure 3**.

Table 2. Antileukemic agents from endophytic fungi.

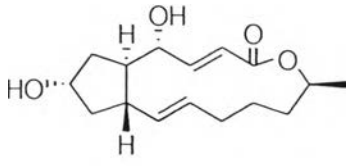
Compound	Cell line (EC_{50})		Endophytic fungus	Host plant	Reference
Brefeldin A [18]	HL-60	10.0 ng/ml	*Aspergillus clavatus*	*Taxus mairei*	(Wang *et al.*, 2002)
			Paecilomyces sp.	*Torreya grandis*	
Altersolanol B [19]	K562	3.7 µg/ml	*Pleospora* sp. IFB-E006	*Imperata cylindrica*	(Ge *et al.*, 2005)
Dactylariol [20]	K562	1.3 µg/ml			
Deoxybostrycin [21]	K562	3.1 µg/ml			
Chaetominine [22]	K562	21.0 nM	*Chaetomium* sp. IFB-E015	*Adenophora axilliflora*	(Jiao *et al.*, 2006)
Penicillenone [23]	P388	1.38 µM	*Penicillium sp.*	*Aegiceras corniculatum*	(Lin *et al.*, 2008)
Emodin [24]	THP-1	-	*Thielavia subthermophila*	*Hypericum perforatum*	(Kusari *et al.*, 2009)
Hypericin [25]	THP-1	-			
9-deacetoxyfumigaclavine C [26]	K562	3.10 µM	*Aspergillus fumigatus*	*Cynodon dactylon*	(Ge *et al.*, 2009)

Table 2. (continued)

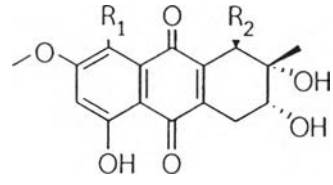
Compound	Cell line (EC_{50})		Endophytic fungus	Host plant	Reference
6-methyl-1,2,3-tri hydroxy-7,8-cyclo hepta-9,12-diene-11 -one-5,6,7,8-tetra lene-7-acetamide [27]	THP-1	30 µg/ml	*Aspergillus sp.*	*Gloriosa superba*	(Budhiraja *et al.*, 2012)
Ergosta-4,6,8(14),22- tetraene-3one [28]	K562	0.35 µg/ml	*Nigrospora sphaerica*	*Vinca rosea*	(Metwaly *et al.*, 2014)
	HL-60	0.03 µg/ml			
Ergosta-7,9(14),22- triene-3β-ol [29]	K562	0.35 µg/ml			
	HL-60	0.39 µg/ml			

Table 2. (continued)

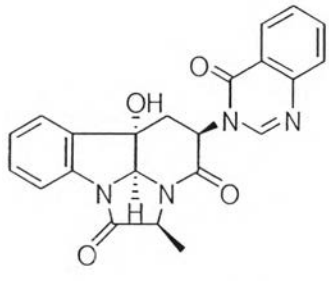
Compound	Cell line (EC_{50})		Endophytic fungus	Host plant	Reference
4-(hydroxymethyl)-3,5-dimethyldihydrofuran-2(3H)-one **[30]**	K562	0.49 µg/ml	*Nigrospora sphaerica*	*Vinca rosea*	(Metwaly *et al.*, 2014)
	HL-60	0.2 µg/ml			
3-(1-hydroxyethyl)-4-methyldihydrofuran-2(3H)-one **[31]**	K562	0.01 µg/ml			
	HL-60	0.4 µg/ml			



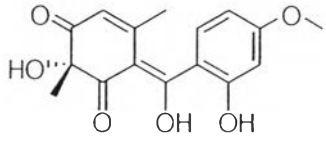
Brefeldin A [18]



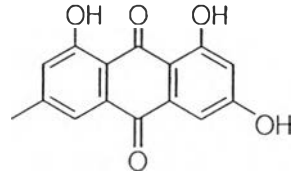
	R_1	R_2
Altersolanol B [19]	H	H
Dactylariol [20]	H	OH
Deoxybostrycin [21]	OH	H



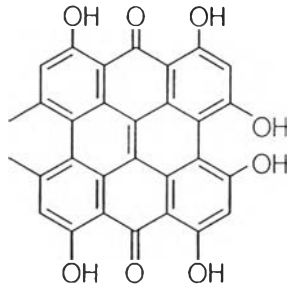
Chaetominine [22]



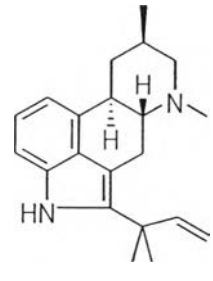
Penicillenone [23]



Emodin [24]

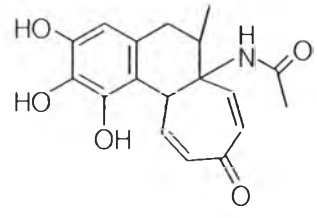


Hypericin [25]

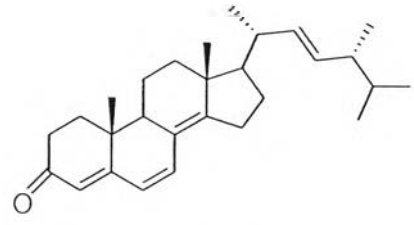


9-Deacetoxyfumigaclavine C [26]

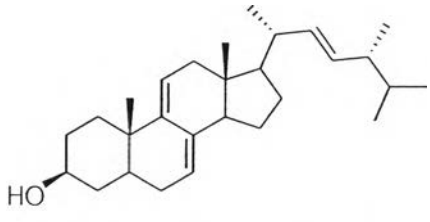
Figure 2. Antileukemic agents from endophytic fungi.



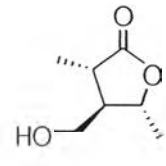
6-Methyl-1,2,3-trihydroxy-7,8-cyclohepta-9,12-diene-11-one-5,6,7,8-tetralene-7-acetamide [27]



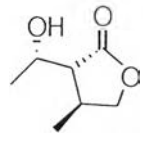
Ergosta-4,6,8(14),22-tetraene-3one [28]



Ergosta-7,9(14),22-triene-3β-ol [29]



4-(Hydroxymethyl)-3,5-dimethyl dihydrofuran-2(3H)-one [30]

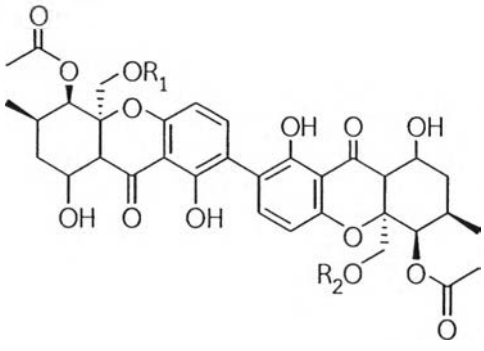


3-(1-Hydroxyethyl)-4-methyl dihydrofuran-2(3H)-one [31]

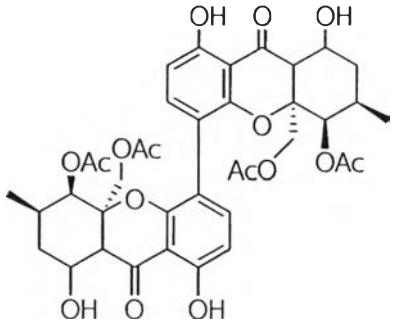
Figure 2. (continued)

Table 3. Anticancer agents from *Phomopsis*.

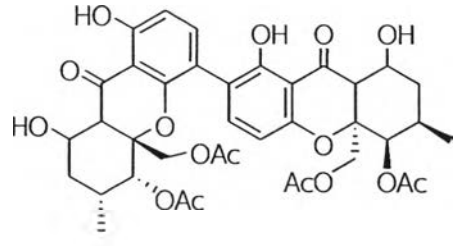
Compound	Cell line	Host plant	Reference
Dicerandrols A-C **[32-34]**	A549, HCT-116	*Dicerandra frutescens*	(Wagenaar and Clardy 2001)
Phomoxanthones A-B **[35-36]**	KB, BC, Vero	*Tectona grandis*	(Isaka *et al.*, 2001)
Phomopsilactone **[37]**	HeLa	*Cassia spectabilis*	(Silva *et al.*, 2005)
Taxol **[1]**	BT220, HL251	*Taxus cuspidata*	(Kumaran and Hur 2009)
2-(7'-hydroxyoxooctyl)-3-hydroxy-5-methoxybenzene acetic acid ethyl ester **[38]**	Hep-2, HepG2	*Excoecaria agallocha*	(Huang *et al.*, 2009)
Oblongolides Y-Z **[39-40]**	KB, BC, NCI-H187, Vero	*Musa acuminata*	(Bunyapaiboonsri *et al.*, 2009)
Phomoarcherins A-B **[41-42]**	KB	*Vanilla albidia*	(Hemtasin *et al.*, 2011)
Pestalotin **[43]**	PC-3, HT-29	*Corylus avellana*	(Akay *et al.*, 2014)
4-butoxy-6-(1-hydroxypentyl)-5,6-dihydro-2H-pyran-2-one **[44]**	MDA-MB-231		



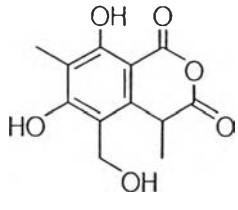
	R_1	R_2
Dicerandrol A **[32]**	H	H
Dicerandrol B **[33]**	Ac	H
Dicerandrol C **[34]**	Ac	Ac



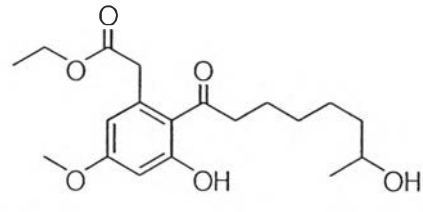
Phomoxanthone A **[35]**



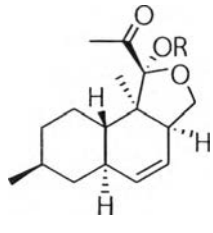
Phomoxanthone B **[36]**



Phomopsilactone **[37]**

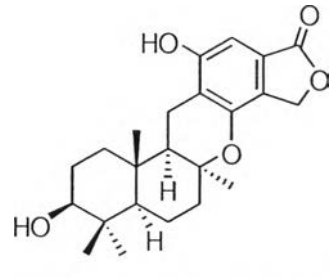


2-(7′-Hydroxyoxooctyl)-3-hydroxy-5-methoxybenzene acetic acid ethyl ester **[38]**



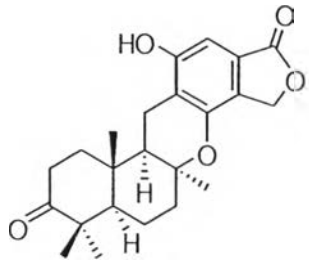
Oblongolide Y **[39]** R = CH_3

Oblongolide Z **[40]** R = CH_2CH_2Ph

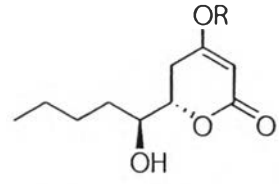


Phomoarcherin A **[41]**

Figure 3. Anticancer agents from *Phomopsis*.



Phomoarcherin B **[42]**



Pestalotin **[43]** R = CH_3

4-Butoxy-6-(1-hydroxypentyl)-5,6-dihydro-2H-pyran-2-one **[44]** R = $CH_2CH_2CH_2CH_3$

Figure 3. (continued)