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Review Article

Fungal Endophytes are Effective Alternatives and Novel Sources of Anticancer Drugs

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Abstract | Natural bioactive molecules or compounds isolated from different living organisms are the rich sources for the novel drugs. Endophytes are the rich source of these bioactive molecules having a wide range of applications as compared to the original products. Fungal endophytes are the most commonly used endophytes for the isolation of various different types of bioactive molecules. These bioactive molecules can be used as antimicrobial, antibacterial and anticancer agents. Fungal endophytes like *Taxomyces andreanae* isolated from Yew plant have the potential to produce an anti-cancer compound called Paclitaxel. Other different fungal endophytic species produce various other types of anticancer compounds like camptothecin, podophyllotoxin, torreyanic acid, vincristine, and vinblastine. This review is organized to describe the general study of natural bioactive molecules or secondary metabolites secreted by fungal endophytes as novel sources of anticancer drugs. The main purpose of this review is to organize the effective compound of the fungal endophytes for cancer treatments.

Novelty Statement | Endophytes are the ridiculous source of the bioactive molecules and Fungal endophytes are most frequently used. The current review article organized the origin, function of endophytes and secondary metabolite with their basic properties.

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Introduction

The discovery of natural products has played a major role in the search for the novel drugs, these natural products are the chemical compounds isolated from different living organisms. Organisms including animals, plants, marine-macro organisms like algae, sponge and corals and microorganisms like bacteria, fungi, and actinomycetes are the prominent source of novel natural products. These natural products can be the source of discovery for novel bioactive molecules that have therapeutic use with much better pharmacological and pharmaceutical properties than the original compounds (Sudha *et al.*, 2016).

Endophytes are the microorganism that forms inconspicuous infection within the plants for the whole or some part of their life cycle and is the rich source of natural bioactive metabolites (Barbara and Christine, 2006). Endophytic bacteria including actinomycetes and endophytic fungi can inhabit the different organs of plants (Arunachalam and Gayathri, 2010). Endophytes can synthesize a wide variety of novel bioactive metabolites that can be used either indirectly or directly as a therapeutic agent for various diseases (Cragg and Newman, 2005). The bioactive metabolites produced by endophytic fungi

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include alkaloids, steroids, phenols, quinones, coumarins, flavonoids, xanthones, and others. These metabolites have shown their activities as antibacterial, antifungal, anticancer, antioxidants, anti-parasitic, insecticidal (Kaul *et al.*, 2012).

Cancer is the group of diseases that causes the uncontrolled and abnormal growth of the different type of respective cells and forms an abnormal cell mass called a tumor. Cancer is the disease that stands second to cardiovascular diseases in its case fatality among chronic non-communicable diseases (Bonita *et al.*, 2006). Approximately 9.6 million deaths estimated to occur due to cancer in 2018, 70% of which occurred in low and middle socioeconomic countries (Sarvesha *et al.*, 2017). Cancer is caused by both extrinsic factors (tobacco, alcohol, smoking, unhealthy diet, lifestyle, environmental factors like exposure to UV or ionizing and non-ionizing radiations) and intrinsic factors (aging, genetic mutation, hormonal disturbance, and poor immune system) that trigger the activation or inactivation of certain genes subsequently leading to abnormal growth of cells (Pandi *et al.*, 2013). Most of the anticancer therapeutic agents or drugs were unable to differentiate between abnormal and normal cells, so researchers try to develop some new anticancer drugs that are more targeted to the abnormally proliferating cancerous cells and have minimal effects on normal cells. Since the discovery of fungal endophyte *Taxomyces andreanae* from Yew plant, by Strobel *et al* (Stierle *et al.*, 1993), the search for anticancer endophytic fungi from different plants brought significant attention of researchers in last 2 decades. Fungal endophytes have harbored the wide range of metabolites like paclitaxel, Xanthones, Ergoflavin, Lignin, Torreyanicacid, Vincristine, Camptothecin, Podophyllotoxin, etc. (Firodiya and Tenguria, 2016). These compounds are known for their anticancer, antiproliferative and antitumor activities.

Endophytes

The word "endophyte" derive from the Greek word "Endon" means within and "phyton" means plants. Endophytes, by definition, are the microorganism that resides asymptomatically under the epidermal cell layer of plants, apparently causing no harm to plants and are the rich source of bioactive natural products (Pimentel *et al.*, 2011). Endophytes found ubiquitously in all plant species forming a communalistic or mutualistic association with respective plants, about 300,000 plant species existing on earth harbors one or more endophytes (Song *et al.*, 2004; Strobel, 2003). The term "endophyte" was first proposed in 1866 (Bary, 1866). Since endophytes were described in Lolium temulentum (Darnel) (EM Freeman, 1904), they were isolated from different organs of plants species of equisetopsids, hornworts, lycophytes, mosses, ferns, spermatophytes and liverworts from the arctic to tropic, and from the agricultural to wild ecosystems (Arnold, 2007; Stone *et al.*, 2000). Endophytes enhance ability of host plants to resist against herbivores (Brem and Leuchtmann, 2001), insects (Breen, 1994), diseases (Clay, 1990), drought, (Malinowski *et al.*, 1997) plant pathogens (Kharwar *et al.*, 2011)and also give resistance against temperature and salinity (Redman *et al.*, 2001).

Use of secondary metabolites in chemotherapy for the treatment of cancer

Currently available data revealed that about 60% of anticancer drugs were derived from natural products or their derivatives. Over 40 years ago, the National Cancer Institute started a program in which higher plants considered as the key source for the production of anti-cancer agents (Clark, 1996). Just like an antibiotic, microbes are also able to produce anti-tumor compounds as secondary metabolites, which are significant in chemotherapy to treat different kinds of cancers (Tomasz, 1995). Some examples of antitumor agents produced by microbes are Actinomycin D, Mitomycin, Bleomycin, Anthracyclines, Daunorubicin, Doxorubicin, and Taxol, that are used in the treatment of different kinds of tumors (Wall and Wani, 1995).

Endophytic fungi as a source of novel bioactive metabolites

The fungi that colonize asymptomatically within the plants are endophytic fungi and were known since the late 19th century (Guerin, 1898). About 1.5 million fungal species exist on earth; only 100,000 are known so far (Hawksworth, 2001). Fungal endophytes colonizes the different organs of plants and were isolated from the aerial parts of plant and root complexes from wide range of hosts including, angiosperms (Davis *et al.*, 2003), gymnosperms (Hormazabal and Piontelli, 2009; Schmeda-Hirschmann *et al.*, 2005), bryophytes (Zhang *et al.*, 2013), algae (Wang *et al.*, 2006) and pteridophytes (Zhang *et al.*, 2004). Fungal endophytes reported to be isolated from plants in Arctic (Arnold and Lutzoni, 2007) Antarctic (Rosa *et al.*, 2009) geothermal soils (Appoloni *et al.*, 2008)rainforest (Banerjee, 2011) desert (El-Deeb *et al.*, 2013) mangrove (Thatoi *et al.*, 2013) and forests (Sutjaritvorakul *et al.*, 2011).

The natural products and bioactive molecules produced by endophytes possess unique bioactivities and structures, representing a reservoir that offers a huge potential for exploitation in pharmaceutical and pharmacological industries to make an effective drug against various infections and cancer (Tan and Zou, 2001). Currently, available data shows that more than 40 percent of new bioactive molecules were obtained in a period of the last two and half decades and half of them were derived from a microorganism. Studies also revealed that about 60% of anticancer and 70% antimicrobial drugs used as clinical treatment of various diseases are natural products or natural product derivatives (Omeje *et al.*, 2017; Cragg and Newman, 2005). The bioactive secondary metabolites isolated from the different endophytic fungi have shown anticancer, antimicrobial, insecticidal and antioxidant activities (Kaul *et al.*, 2012; Tan and Zou, 2001). The

secondary metabolite and their properties shown in Table 1. These secondary metabolites are produced by an organism in response to external stimuli like foreign infection or nutritional changes (Ryan *et al*., 2008). The bioactive metabolites produced by fungal endophytes are far more in number than that of other endophytic microbes (Zhang *et al*., 2006).

Table 1: Secondary metabolites produced by endophytic fungi in the host plants.

Endophytic fungi	Host plant	Secondary metabolite	Property of metabolite
Taxomyces andreanae	*Taxus brevifolia*	Paclitaxel	Anticancer
Aspergillus fumigatus TXD105	*Taxodium distichum*	Paclitaxel	Anticancer
Alternaria tenuissima TER995	*T. arhuna*	Paclitaxel	Anticancer
Bartalinia robillardoides Tassi	*Aegle marmelos* Correa ex Roxb	Paclitaxel	Anticancer
Pestalotiopsis microspore EF01	*Plectranthus amboinicus*	Paclitaxel	Anticancer
Fusarium lateritium	*Taxus baccata*	Paclitaxel	Antitumor
Pestalotiopsis guepinii	*Wollemia nobilis*	Paclitaxel	Antitumor
P. microspore	*Taxus wallichiana*	Paclitaxel	Anticancer
Alternaria sp.	*Ginkgo biloba*	Paclitaxel	Antitumor
Cladosporium cladosporio	*Taxus media*	Paclitaxel	Antitumor
Pestalotiopsis microspore	*Taxodium distichum*	Paclitaxel	Antitumor
P. terminaliae	*Terminalia arjuna*	Taxol	Anticancer
Phyllosticta citricarpa	*Citrus medica*	Paclitaxel	Antitumor
Tubercularia sp.	*Taxus mairei*	Paclitaxel	Anticancer
Pestalotiopsis pauciseta	*Cardiospermum helicacabum*	Paclitaxel	Antitumor
Entrophospora infrequent	*Nothapodytes foetida*	Camptothecin	Antitumor
Fusarium oxysporum	*Rhizophora annamalayana*	Taxol	Anticancer
Fusarium redolens	*Taxus baccata*	Taxol	Anticancer
Fusarium solani	*Camptotheca acuminate*	Camptothecin	Anticancer
Trichoderma atroviride LY357	*C. acuminate*	Camptothecin	Anticancer
Nodulisiporium sp.	*Nethapodytes fortida*	Camptothecin	Anticancer
Fusarium solani	*Apodytes dimidiate*	Camptothecin	Anticancer
Aspergillus fumigatus	*Juniperus communis*	Podophyllotoxin	Antitumor
Fusarium oxysporum	*Juniperus recurve*	Podophyllotoxin	Antitumor
Phialocephala fortinii	*Sinopodophyllum hexandrum*	Podophyllotoxin	Anticancer
Alternaria sp.	*Sabina vulgaris*	Podophyllotoxin	Anticancer
Mucor fragilis (TW5)	*Sinopodophyllum hexandrum*	Podophyllotoxin	Anticancer
Penicillium implicatum	*Diphylleia sinensis*	Podophyllotoxin	Anticancer
Trametes hirsute	*Podophyllum hexandrum*	Podophyllotoxin	Antitumor
Penicillium implication	*Dysosma veitchii*	Podophyllotoxin	Antitumor
Phialocephala fortinii	*P. peltatum*	Podophyllotoxin	Antitumor
Alternaria neesex	*Sinopodophyllum hexandrum*	Podophyllotoxin	Antitumor
Phialocephala fortinii	*Podophyllum peltatum*	Podophyllotoxin	Antitumor
Chaetomium sp. IFB-E015	*Adenophora axilliflora*	Chaetominine	Anticancer
Fusarium oxysporum	*Catharanthus roseus*	Vincristine	Antitumor
A. alternata KT380662	*Passiflora incarnata L*	Flavone Chrysin	Anticancer Hepatoprotective
Cephalotheca faveolata	*Eugenia jambolana Lam*	Sclerotiorin	Antiproliferative
Chaetomium globosum IFB-E019	*Imperata cylindrical*	Chaetoglobosin U	Cytotoxic
C. globosum L18	*Curcuma wenyujin*	Chaetoglobosin X	Cytotoxic
Penicillium brasilianum	*Melia azedarach*	Phenylpropanoids	Anticancer
Dichotomomyces albus	*D. cejpii*	Xanthocillin X	Anticancer
Pestalotiopsis microspore	*T. taxifolia*	Torreyanic acid	Anticancer

Endophyte-host interaction

A special mechanism adopted by endophytes to penetrate and survive inside the host tissues. Endophytes carry exo-enzymes, which are necessary for the colonization, and apoplastic-washing fluid inside the host is essential for its growth. The mutualistic association is developed when endophyte colonizes the roots of the plant. Roots help to provide proper nourishment to endophyte, so they make a strong association. Some studies confirm that the metabolites released by the plants for its defense are not enough to overcome the pathogenic effect of pathogens (Schulz *et al*., 2002). In the presence of these factors, the equilibrium between host defense and fungal pathogenesis generated (Figure 1). The disease may result when that equilibrium was disrupted. A counter metabolite secreted by the endophyte to overcome the effect of epiphyte, which helps in colonization. Such interaction may lead to the synthesis of secondary metabolites (Priti *et al*., 2009).

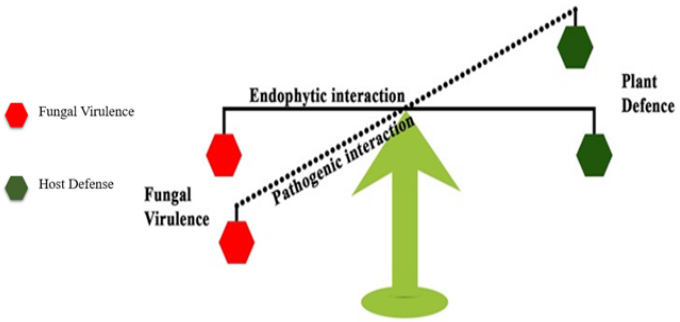


Figure 1: The equilibrium relationship between the host plant defense and endophytic fungi. Adopted from (Chandra, 2012).

Anticancer compounds derived from endophytic fungi

For the discovery of novel anticancer compounds plants, endophytic fungi may be the main source of natural lead bioactive secondary metabolites that are cytotoxic in nature. About 19 different types of chemical classes of fungal secondary metabolites have been identified that have shown their anticancer properties against 45 different cell lines (Bano *et al*., 2016). Some of the natural lead anticancer compound isolated from endophytic fungi are paclitaxel, podophyllotoxin, camptothecin, ergoflavin, swainsonine, sclerotiorin, flavone chrysin, torreyicacid, vincristine, and vinblastine.

Paclitaxel: ($C_{47}H_{51}NO_{14}$)

Paclitaxel (Taxol) is the complex diterpenoid compound and is the most effective antitumor and anticancer agent develop in the past 30-40 years (Pandi *et al*., 2013). For the first time, Taxol was isolated from the inner bark of Pacific Yew plant, *Taxus brevifolia* (Wani *et al*., 1971), a traditional medicinal plant used by native Americans (Stierle *et al*., 1995). The most common and significant source of Taxol are the bark of the Yew trees that belongs to Taxus genus but unfortunately, these trees are rare, slow grower and a large amount of its bark need to be processed to obtain a small yield of Taxol (Kusari and Spiteller, 2012). The first Taxol producing endophytic fungi, *Taxomyces andreanae* was isolated from *Taxus brevifolia* in early 1990s. Since then, Paclitaxel has been isolated from more than 50 endophytic fungi by different scientist and researcher all over the world (Hao *et al*., 2013). Some of them that produce Paclitaxel is *Taxomyces andreanae* (Wani *et al*., 1971); *Taxodium distichum* (Li *et al*., 1996); *Wollemia nobilis* (Strobel *et al*., 1997); *Bartaliniaro billardoides* (Gangadevi and Muthumary, 2008); *Pestalotiopsis terminaliae* (Gangadevi and Muthumary, 2009); *Taxus wallichiana* (Wang *et al*., 2000); *Phyllosticta spinarum* (Senthil Kumaran *et al*., 2008b); *Botryodiplo diatheobromae* (Pandi *et al*., 2010) and *Didymostilbe* sp., (Wang and Tang, 2011). *Aspergillus fumigatus TXD105*, isolated from *T. distichum* (Ismaiel *et al*., 2017); *Alternaria tenuissima TER995*, isolated from *T.arhuna* (Ismaiel *et al*., 2017) and *Bartalinia robillardoides Tassi* isolated from A*egle marmelos Correa ex Roxb* (Gangadevi and Muthumary, 2008) were capable of producing paclitaxel. Endophytic fungi belong to different genera like *Alternaria alternata, Pestalotiopsis microspora, Periconia* sp., *T. andreanae*, *Chaetomella raphigera, Pithomyces* sp., *Monochaetia* sp., and *Seimatoantlerium nepalense, reported* to produce Taxol (Visalakchi and Muthumary, 2010). Most of the paclitaxel producing strains were isolated from Taxus plants.

In 1992, Paclitaxel was approved by the FDA for the treatment of ovarian cancer (Cremasco *et al*., 2009). Its use is then extended to the treatment of a variety of cancer including ovarian cancer, head and neck carcinoma, lung cancer, breast cancer, AIDS-related Kaposi's sarcoma. (Cremasco *et al*., 2009; Wall *et al*., 1976; Suffness, 1995; Pandi *et al*., 2013). Taxol inhibits cancer cell proliferation by promoting the polymerization of tubulin and stabilizing the depolymerization of tubulin (Aly *et al*., 2010; Visalakchi and Muthumary, 2010). Paclitaxel has also been used against non-cancerous diseases including the prevention of restenosis (Christian Herdeg *et al*., 2000) neurodegenerative diseases and polycystic kidney disease.

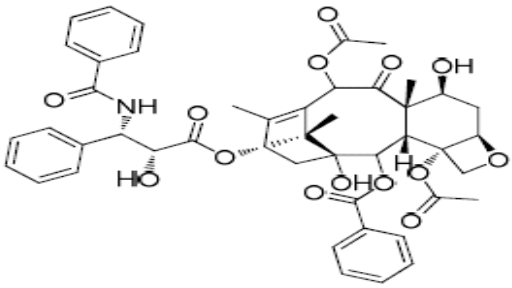


Figure 2: Paclitaxel

Camptothecin: ($C_{20}H_{16}N_2O_4$)

Camptothecin is a Penta-cyclic quinolone alkaloid isolated from *Entrophosporain* frequent, an endophytic

fungus of the host plant, *Nothapodytes foetida* (Puri *et al.*, 2005). The compound is a potent antineoplastic agent that serves as the precursor for the synthesis of two anticancer drugs named as topotecan and irinotecan (Shaanker *et al.*, 2008; Bhanot *et al.*, 2011). These compounds were also extracted from endophytic fungi *Fusarium solani* inhabiting *Camptotheca acuminate* (Kusari *et al.*, 2009). Camptothecin exerts its cytotoxic effect on the cancerous cell by inhibiting the dissociation of the DNA-topoisomerase 1 complex during replication (Pommier, 2006). These compounds showed cytotoxic effect against human liver and ovarian cancer cell lines, thus can be used for the treatment of lungs and ovarian cancer (Puri *et al.*, 2006). Camptothecin as shown its cytotoxic activity against lung cancer, ovarian cancer, and liver cancer.

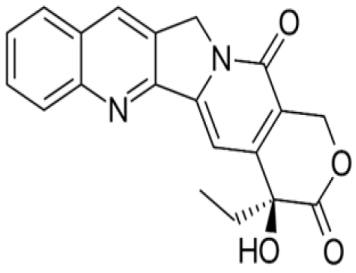


Figure 3: Camptothecin

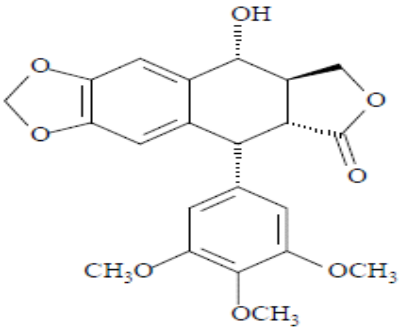


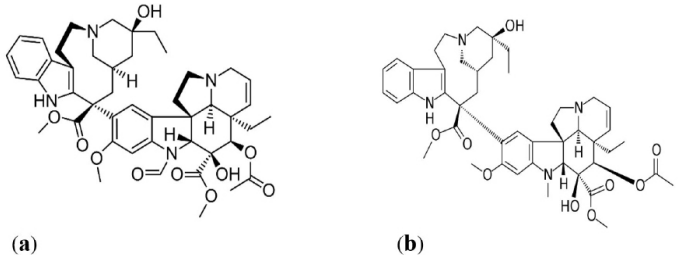
Figure 4: Podophyllotoxin

Podophyllotoxin: ($C_{22}H_{22}O_8$)

Podophyllotoxin is the non-alkaloid lignin and their analogs may be clinically used as anticancer and antiviral drugs, moreover, they are the precursor of many anticancer drugs like teniposide ($C_{32}H_{32}O_{13}S$) and etoposide ($C_{29}H_{32}O_{13}$) (Kour *et al.*, 2008; Eyberger *et al.*, 2006b). Various endophytic fungi are the rich source of podophyllotoxin such as *Aspergillus fumigatus* isolated from *Juniperus communis* (Kusari *et al.*, 2009; Eyberger *et al.*, 2006a); *Fusarium oxysporum* isolated from *Juniperus recurva* (Kusari *et al.*, 2009); *Phialocephala fortinii* isolated from *Podophyllum peltatum* (Eyberger *et al.*, 2006a) *Trametes hirsute* from *Podophyllum hexandrum* (Puri *et al.*, 2006) and *Phialocephala fortinii from P. peltatum* (Puri *et al.*, 2006). The cytotoxicity of the podophyllotoxin and other related compound is due to abilities of these compounds to inhibit topoisomerase II, thus blocking the ligation step in of cell cycle, harming the genome and eventually lead to cell death and apoptosis (Cragg and Newman, 2009; Gordaliza *et al.*, 2004).

Vincristine ($C_{46}H_{56}N_4O_{10}$) and vinblastine ($C_{46}H_{58}N_4O_9$)

Vincristine and Vinblastine are indole alkaloids, well known for their cytotoxic activities (Zhang *et al.*, 2012). Vincristine is an alkaloid having cytotoxic effects and was originally isolated from endophytic fungi inhabiting *Catharanthus roseus* (Yang *et al.*, 2004). This drug has shown its significant ability to be used as a chemotherapeutic agent in acute nephroblastoma and lymphoblastic leukemia (Puri *et al.*, 2018). Vincristine binds to spindle proteins and microtubules irreversibly in the S phase of the cell cycle. It interferes with the formation of the mitotic spindle and results in tumor cell arrest in metaphase (Kharwar *et al.*, 2011). The action mechanism of Vinblastine is the disruption of intracellular transport, interfering with the microtubule and mitotic spindle dynamics and decreases the tumor blood flow (Zhang *et al.*, 2012; Moore and Pinkerton, 2009).



(a) **(b)**

Figure 5: (a) Vincristine (b) vinblastine

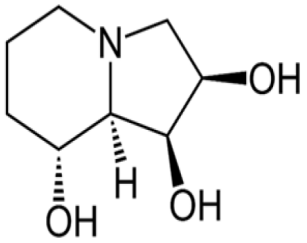


Figure 6: Swainsonine

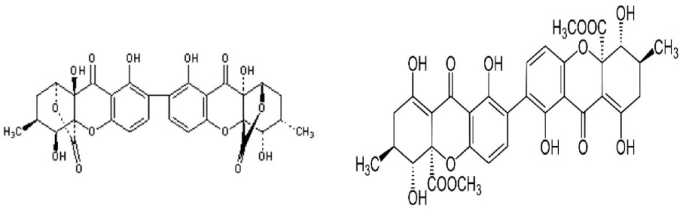
Swainsonine

Swainsonine, anindolizidine alkaloid was first isolated and identified from *Swainsona canescens* (Colegate *et al.*, 1979). Hino *et al* (Hino *et al.*, 1985) in 1985 for the first reported that Swainsonine inhibits the proliferation of tumor cells and metastasis. Swainsonine is produced by endophytic fungi including the Alternaria sect. *Metarhizium anisopliae* ,*Slafractonia leguminicola* and *Undifilum oxytropis* (Ren *et al.*, 2017). Swainsonine is a specific inhibitor of α-mannosidase II in Golgi bodies, thus affects the synthesis of glycoproteins, glycolipids, and carbohydrates, therefore, promotes the apoptosis of tumor cells (Ren *et al.*, 2017). Various researcher has shown their ability as anticancer and antitumor activity against Ehrlich

ascites carcinoma (Santos *et al.*, 2011), colorectal cancer (Hamaguchi *et al.*, 2007), lymph cancer (Goss *et al.*, 1994), leukemia (Singh and Kaur, 2014) and human hepatoma (You *et al.*, 2012).

Ergoflavin ($C_{30}H_{26}O_{14}$)

Ergoflavin, a dimeric xanthene linked at position-2, belongs to the compound of the class "ergochrome" and family Sapotaceae. Ergoflavin is the novel anticancer agent originally isolated from the ergot fungus *Claviceps purpurea* and then from *Penicillium oxalicum*, *Pyrenochaeta terrestris*, *Phoma terrestris* and *Aspergillus sp* as well (Deshmukh *et al.*, 2009). Endophytic fungus growing in the leaves of the Indian medicinal plant called *Mimusops elengi* is also capable of synthesizing Ergoflavin (Deshmukh *et al.*, 2009). Another similar compound belonging to ergochrome is Secalonic acid D ($C_{32}H_{30}O_{14}$), a mycotoxin isolated from mangroves endophytic fungus; possess anticancer properties against K562 and HL60 cells by inducing apoptosis (Zhang *et al.*, 2009a). Ergoflavin significantly inhibits IL-6 and TNF-α (Lunardelli Negreiros de Carvalho *et al.*, 2016).



(a) (b)

Figure 7: (a) Ergoflavin (b) Secalonic acid D

Flavone chrysin (5, 7-dihydroxyflavone)

Chrysin belongs to the flavone class of 15-carbon poly-phenolic compounds called flavonoids. *A. alternata* KT380662, an endophytic fungus isolated from leaves of *Passiflora incarnata* L. reported to produce FChR. It has significant ability to impart cytotoxic effects on human liver carcinoma cells (HepG2) (Khoo *et al.*, 2010; Seetharaman *et al.*, 2017). Chrysin enhances X-box binding protein-1 splicing and GRP78 overexpression chrysin-induced apoptosis (Sun *et al.*, 2011).

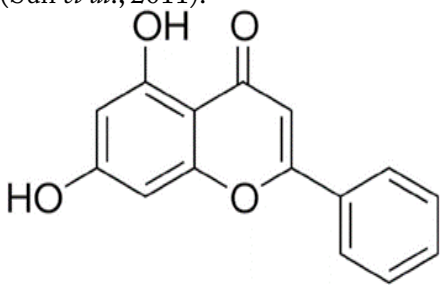


Figure 8: Chrysin (5, 7-dihydroxyflavone)

Xanthocillin X ($C_{18}H_{12}N_2O_2$)

Xanthocillin X, for the first time isolated from *Dichotomomyces albus* attributed to *D. cejpii* (Fang *et al.*, 2006; Bladt *et al.*, 2013; Wu *et al.*, 1989) but it is also been isolated from *Pencillium chrysogenum* (Frisvad *et al.*, 2004; Bladt *et al.*, 2013). It is found to be effective against Ehrlich ascites carcinoma (Zhang *et al.*, 2010). Xanthocillin X also has shown the cytotoxic activity against human cervical cancer, breast cancer, lung cancer, liver cancer, prostate cancer and leukemia (Wu *et al.*, 1989; Li *et al.*, 2012).

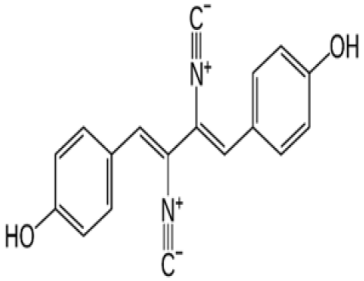


Figure 9: Xanthocillin

Sclerotiorin ($C_{21}H_{23}ClO_5$)

Sclerotiorin, an orange colored pigment is a secondary metabolite produced from an endophytic Fungi called *Cephalotheca faveolata* that is isolated from the leaves of *Eugenia jambolana Lam* (Giridharan *et al.*, 2012). Sclerotiorin originally isolated from a fungus called *Pencillium sclerotiorum* (Curtin and Reilly, 1940) and later on it is isolated from several other fungi.it is an anti-proliferative compound used in the treatment of different type cancer. Sclerotiorin possesses activities like inhibition of Grb2-Sch interaction thus blocking the oncogenic Ras signal (Nam *et al.*, 2000).

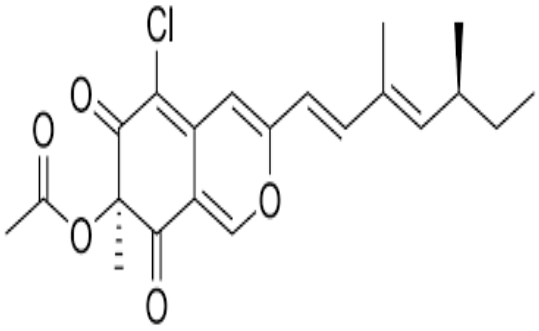


Figure 10: Sclerotiorin

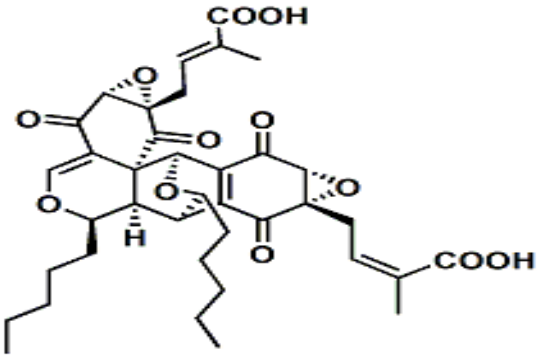


Figure 11: Torreyanic acid

Torreyanic acid ($C_{38}H_{44}O_{12}$)

Torreyanic acid is a dimeric quinone that is isolated from endophytic fungi "*Pestalotiopsis microspore*" inhabiting *T. taxifolia* (Lee *et al*., 1996). Torreyanic acid is about five to ten times more effective in the cell lines that are sensitive to Kinase C protein antagonists and induce apoptosis in the proliferating cells (Lee *et al*., 1996).

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