Endophytes as source of anticancer drugs

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ABSTRACT

Cancer is the loss of control over cell division, apoptotic resistance and invasion into normal tissue. Which is one of the major causes of death worldwide. The increased death rate due to cancer necessitates a challenge to explore new promising, safe, cheap, and less harmful potential drugs with high therapeutic value. Anticancer drugs from natural sources like microorganisms, plants, and animals offer the potential of finding novel compounds with unique bioactivities for cancer treatments. While comparing chemically and naturally synthesized drugs, naturally synthesized drugs are cost-effective and also of high therapeutic value. Endophytes are the kind of microbes that live in the intracellular or intercellular area of a healthy plant. Endophytic fungi inhabiting medicinal plants exhibit a wide array of chemical diversity and also, they modulate the production of specific secondary metabolites in host plants. These endophytic fungi can act as a promising source of several compounds with anticancer activity. The desired metabolites from these endophytes can be manipulated both genetically and physicochemically for increased yield. This chapter emphasizes fungal endophytes producing anticancer metabolites and assesses the interaction between host plant and endophytes that enables the synthesis of novel secondary metabolites. Insight from such a review would provide a new arena of research on fungal endophytes producing novel secondary metabolites as an alternative, reliable, and economical source of anticancer drugs.

Keywords Endophytes. Fungi. Host plant. Secondary metabolites. Anticancer agents

I. INTRODUCTION

Cancer is the uncontrolled growth of abnormal cells beyond their usual boundaries to invade adjacent body parts spread to other organs and eventually spread throughout the body. The loss of division control over cancer cells is the net result of accumulated abnormalities in multiple regulatory systems and that can be distinguished from normal cell behaviour. The process of spreading of cancer over adjoining parts is termed as metastasis and is a major cause of death by cancer. There are hundreds of distinct types of cancer that vary in their behaviour and response to treatment. As a result of carcinogens causing cancer, an exponential rise in the world population having numerous health ailments has been reported (Chakravarty and Gaur 2018). The present therapeutic regime faces challenges such as the emergence of chemoresistance, relapse after treatment and associated adverse effects. This necessitates the investigation of new therapeutic agents of natural origin and to sketch of the underlying mechanism of action (Tyagi et al., 2021). Alternative plans for cancer treatment, are not only meant to cure the malignancy but have minimum or no side effects. Even though the phytochemicals were identified as the source of potential drugs, due to some remarkable challenges the use of plants as a drug molecule source and their use in drug research has recently seen a decline. Plant-based natural drug production is always not up to the desired level, and it is produced under specific environmental conditions, stress at a specific developmental stage or during nutrient availability. The main challenges of using plants as the source of drugs include, a slow growth rate taking several years for product accumulation and extraction, non-reproducibility of the desired phytochemicals and limitations associated vulnerability of plant species (Kala et al., 2006). From various geographical locations and diverse environmental conditions, endophytes have been identified from different plant species and plant parts (Arora and Ramawat 2017). Considering the limitations associated with the use of plant species as a source of drugs, microorganisms act as an inexhaustible, readily renewable, abundant, source of potential therapeutic agents under controlled culture conditions with high biodiversity (Abdel-Razek et al., 2020). The pharmaceutical industry for drug discovery has been using the metabolites produced from plants for more than 30 years (Newman and Cragg, 2020).

Endophytes are microorganisms that reside inside healthy plant tissues and act as substantial sources of potential anti-cancer agents. Host's unique metabolites are defended by endophytes due to their strong tolerance towards it. The transformation ability of many endophytes depends on the detoxification of these highly bioactive molecules and up to a certain extent the same thing determines the colonization range of their host (Wang and Dai 2011). Endophytes have been distributed over a wide range since geographically the isolation process of anticancer activities displayed by the microbes (Chakravarty and Gaur 2018). While we compare the structure types of active compounds produced by endophytes with that of host plants it has been far beyond those produced by host plants (Wang and Dai 2011). Endophytes colonise plant tissues without imparting any negative effects" (Bacon and White 2016). A broad spectrum of pharmacological properties including anticancer, antiviral, antibacterial, and antifungal activity exhibited by secondary metabolites isolated from endophytes (Jalgaonwala et al., 2017). Based on morphological characteristics and intergenic transcribed spacer (ITS) sequences, endophytic microbes are of three categories endophytic bacteria, endophytic fungi and endophytic actinomycetes. Compared with other pathogenic counterparts, fungal endophytes usually reside without showing any disease indication inside the host (Swamy et al., 2016). Fungal endophytes exhibit an ample number of medicinal properties such as anti-tumour, anti-bacterial, anti-viral, immunostimulatory and anti-inflammatory (Bedi et al., 2017; Mishra et al., 2011). So far less than 16% of the fungal species described have been cultured and studied. Less than 5% of the total fungal species represent a large source of characteristic bioactive metabolites (Bedi et al., 2018). Fungal species richness is estimated to be around 2.2 to 3.8 million globally (Hawksworth and Lücking 2017)

Among the available anti-cancer drugs, many of them show toxicity towards normal proliferating cells and cause adverse effects, and also, they are less effective against distinct types of cancer, which results in the need for other natural bioactive compounds (Remesh, 2017). A broad range of bioactive molecules such as alkaloids, quinones, flavonoids, terpenoids, steroids etc., and others with unique structures and a number of pharmacological properties are provided by endophytic fungi (Gouda et al., 2016). Many human cancer treatments involve the clinical use of plant-derived anticancer drugs such as Taxol, vinblastine, vincristine, etoposide, topotecan etc (Balunas and Kinghorn, 2005). This chapter summarises the novel secondary metabolites used as anti-cancer drugs produced by fungal endophytes and cytotoxicity towards particular cancer cell lines and the interaction between microbe and host resulting in this whole process, along with the structure of some major anticancer compounds. The aim of this chapter is to highlight the new area of research on fungal endophytes producing potential anticancer metabolites as a source of anticancer drugs.

ENDOPHYTIC ACTINOMYCETES

Actinomycetes of various genera associated with various parts of plants are termed endophytic actinomycetes. They are one of the most promising sources of novel bioactive compounds having pharmaceutical and agricultural importance. A wide range of bioactivities such as antiviral, anti-cancer, antimicrobial and antioxidant properties are shown by purified compounds and crude extracts from endophytic actinomycetes. (Prashith Kekuda 2016). More than 50,000 bioactive secondary metabolites were produced by actinomycetes. Comparatively, a smaller number of endophytes were reported from medicinal plants by comparison with those from soil and marine (Zhang et al., 2014). *Amycolatopsis* sp. A00066 and A00089, are actinomycetes isolated from *Camptotheca acuminate*, and *Taxus chinensis* respectively are two antioxidants producing actinomycetes first reported by Wu et al. (Wu et al., 2009). Due to the higher effectiveness in antitumor response and lower side effects of endophytic extracts, they are safer alternatives to chemotherapeutic agents. A number of compounds that are cytotoxic to tumour cells or cancer cell lines have been isolated from endophytic actinomycetes (Banyal et al., 2021). Some actinomycetes produce glucanase that is able to promote plant growth and also inhibit the growth of *Pythium aphanidermatum* (El-Tarabily et al., 2010). Actinomycetes are extensively distributed microorganisms in the environment, they produce bioactive compounds against phytopathogens (Xue et al., 2013; Zeng et al., 2013). Streptomyces is the largest genus among the actinomycetes and they belong to the family Streptomycetaceae (Kämpfer 2006). Two biphenyls: 3′ -hydroxy-5-methoxy-3,4- methylenedioxybiphenyl (1) and 3′ -hydroxy-5,5′ -dimethoxy-3,4- methylenedioxybiphenyl (2) isolated by the fractionation of the crude extract from the culture medium of Streptomyces sp. BO-07 had antibacterial activity against Gram-positive bacteria and antioxidant and strong anticancer activities (Taechowisan et al., 2017)

BACTERIAL ENDOPHYTES AS A SOURCE OF ANI-CANCER DRUGS

Bacterial endophytes show beneficial effects like enhancement of biological N2-fixation, solubilization of phosphate, inhibition of ethylene biosynthesis in response to stresses and production of phytohormones and they also have biocontrol activity (Singh et al., 2017). Co-cultivation method can be used for the generation of desired metabolite from plant organ culture with defined endophytes. Co-cultivation is otherwise known as the co-culture of microorganisms. That is for example culture of two fungal or bacterial strains exploited for large-scale production of desired metabolites (Bertrand et al., 2014). Co-culturing of the endophytic fungus *Aspergillus versicolor* KU258497 and bacterium *Bacillus subtilis* 168 trpC2 results in the formation of two new derivatives of 3,4-dihydronaphthalen-(2 H)-1-one (1-tetralone). One compound aspvanicin B shows cytotoxicity against mouse lymphoma cell line L5178Y at a moderate rate (Abdelwahab et al., 2018). As a result of several studies, it was clear that endophytic bacteria can share compounds with their host. For example, the stem extract of *Alternanthera brasiliana* (Amaranthaceae) contains antimicrobial compounds from the oxylipin family and the authors concluded that the antimicrobial oxylipins present in the host plant were obtained from their bacterial endophytes (Trapp et al., 2015). From different tissues of *Dracaena cochinchinensis* Lour. (a traditional Chinese medicine known as dragon's blood), More than 300 bacteria and actinobacteria were isolated, they belong to the genera Tsukamurella, Arthrobacter, Nocardiopsis, Brevibacterium, Brachybacterium, Kocuria, Nocardioides, Nocardia, Rhodococcus, Pseudonocardia and Streptomyces. These 17 strains that have anthracyclines production and antimicrobial activities also showed cytotoxic and antifungal activities against human cancer cell lines, MCF-7 and Hep G2 (Dudeja and Giri 2014; Salam et al., 2017).

Besides all this, some other examples of endophytic bacteria with anti-cancer properties are pointed out below. Ginsenosides are known for their anticancer property, Ginseng (*Panax ginseng*) is typically characterized by the presence of Ginsenosides. A high concentration of ginsenoside was shown by *Paenibacillus polymyxa*, an endophytic bacteria of Ginseng leaf. Enhanced plant growth and the concentration of ginsenosides were obtained on inoculation of this bacterial strain to Ginseng plants through foliar applications combined with irrigation (Gao et al., 2015). For the functioning of some neoplastic cells, L-asparaginase catalyzes the conversion of L-asparagine. In children and adults with acute lymphoblastic leukaemia, L-Asparaginase introduced to the multi-drug chemotherapy resulted in improvement and complete remission in the majority of the patients (Jakubas et al., 2008). Efficient production of L-asparaginase exhibited by *B. pseudomycoides, Paenibacillus denitriformis* and *B. licheniformis* (Joshi and Kulkarni 2016).

Crude extracts from the metabolite profiling of *Pseudomonas cichorii, Arthrobacter pascens* and *Bacillus safensis* revealed the presence of anticancer and/or antibacterial agents such as crinamidine, angustine, lycorine, powelline and vasicinol. Similarly, the crude extract from *C. macowanii* leaves can biosynthesize bioactive compounds and be bioprospected for the medical application into antibacterial and anticancer agents (Sebola et al., 2020). *Pseudomonas putida* produces an enzyme called l-methioninase shows anticancer activity against leukemia cell lines, lung A549, prostate PC3, liver HepG2, colon HCT116 and breast

MCF-7 (Selim et al., 2015; Selim et al., 2016). 43% cell reduction at 100 µg/mL against A549 lung carcinoma cells was shown by *Raoultella ornithinolytica* endophyte, crude extract. Anti-cancer activity against, the human endometrioid ovarian cancer line (TOV 112D ATCC CRL-11731), human breast adenocarcinoma line (T47D ECACC 85102201) and HeLa cell line was displayed by Protein complex from *R. ornithinolytica*, which results in a reduction in the cell number and cytopathic effect (Fiolka et al., 2013, Fiolka et al., 2015). Lycorine is a secondary metabolite that possesses antibacterial activity, cytotoxic and antitumor activities (Khalifa et al., 2018). As a justification for the statement that endophytes can metabolize secondary metabolites from the host plant, crude extracts of several bacterial endophytes such as *Arthrobacter pascens Bacillus safensis* and *Pseudomonas cichorii* show the presence of lycorine (Ludwig-M¨uller 2015).

FUNGAL ENDOPHYTES AS A SOURCE OF ANTI-CANCER DRUGS

Natural products from endophytic fungi have been identified as the source of anticancer drugs that are able to make a greater impact on modern medicine. In search of a safe reliable drug using natural products, endophytic extracts were screened for antibacterial and cytotoxic activity. As a result, almost 72% of the extract showed cytotoxic activity against one of the tested cell lines, and with >50% growth inhibition 39% of the extracts were active against all the tested cell lines (Katoch et al., 2017). An endophytic fungus of *Cupressus torulosa* (*Pestalotiopsis neglecta* BAB-5510) is considered one of the promising sources of flavonoids, terpenoids, alkaloids, tannins, saponin and carbohydrates (Sharma et al., 2016). *M. citriodora* is an endophytic fungus with a higher anticancer and antimicrobial activity (Katoch et al., 2017). OSMAC-like techniques can make the process of using fungi as a source of bioactive molecules worth it. OSMAC (one strain-many compounds) is an effective strategy, in which the production of diverse bioactive metabolites by varying different cultivation parameters techniques was used in it. This is an important tool that can be used in the large-scale production of the same or different metabolites by activating different silent biogenetic gene clusters of the fungi (Pan et al., 2019). Usually, fungal endophytes are useful to plants but there is also fungus that is having a neutral effect on host plants that is, neither beneficial nor harmful to the host (Backman and Sikora 2008). Some others become active only under certain conditions, that is, endophytes will exist in a latent state with the host ((Granados et al., 2020).

Capsaicin is used as a medicine to relieve pain and also as an anticancer agent for several types of human cancers, It is a bioactive compound found in red and chilli peppers. An endophytic fungus called *Alternaria alternata* isolated from *Capsicum annum*, produces capsaicin (Devari et al., 2014; Clark and Lee 2016). From another report endophytic fungi such as *Juniperus communis* L., Horstmann, *Phialocephala fortinii* and *Trametes hirsuta* as the potential source of podophyllotoxin were isolated from plants with anticancer potential *Juniperus recurve* and *Podophyllum peltatum* (Ardalani et al., 2017). Three mellenin derivatives isolated from the *Penicillium* sp. from *Senecio favus* 6-hydroxymellein (19), 5-methylmellein (18) and 4-hydroxymellein (20) showed cytotoxicity against MCF-7 cancer cell line with IC50 values of, 6.1 mg/mL, >10 mg/mL and 8.3 mg/mL, respectively (Elkhayat and Goda 2017). Alterfungin, a chiral isomer of cladosporol A, shows antitumor activity in mice with gastric cancer xenografts (Chen et al., 2009). Fumiquinazoline C are the bioactive isolates from *Aspergillus fumigatus* endophytes of liverwort *Heteroscyphus tener* (Steph.) Schifn. Shows anticancer activity against the human lung adenocarcinoma epithelial cell line (A549), human prostate cancers PC3, human lung cancer cell line (NCI-H460) and multiple drug resistance PC3D cells (Xie et al., 2015). Hycamin is the water-soluble derivative of camptothecin, which is approved as a potential anticancer agent against ovarian cancers (Manci et al., 2011).

ANTI-CANCER SECONDARY METABOLITES PRODUCED BY FUNGAL ENDOPHYTES

Natural products remain the source of almost half of the drugs available currently and in the case of cancer, it is 60%. The great biological potency and higher structural complexity of natural compounds is the reason behind this. Independent of the host tissues, endophytes inhabiting medicinal plants mimic the production of bioactive compounds and exhibit anti-malarial, anti-cancer and antioxidant pharmacological activities (Khan et al., 2017). There are a number of studies dealing with the fungal diversities in medicinal plants (Dhayanithy et al., 2019; Biswas et al., 2020; Wang et al., 2016)

Biologically active secondary metabolites synthesized by fungal endophytes are flavonoids, phenolic acids alkaloids, quinones, chinones, xanthones, benzopyranones, tetralones, steroids, terpenoids, etc. (Tan and Zhou 2001; Swamy et al., 2016). The milestone for the exploration of natural secondary metabolites from endophytes starts with the discovery of the Taxol-producing fungus *Taxomyces andreanae* from the Pacific yew *Taxus brevifolia* (Stierle et al., 1993). Some extracts of fermentation broth of endophytes for example, the CHCl3 extract of *Pantoea agglomerans from Prunella vulgaris* had potent activity against liver cancer cell line HepG2 with an IC50 of 0.12 µg/mL. that is besides secondary metabolites these also show toxicity towards cancer

cells (Hsieh et al., 2009). Species of the Ascomycetes produce a fungal metabolite called Brefeldin A (Seehafer et al., 2013). It has been reported that Brefeldin A possesses anticancer activity and different cancer cell lines can be used to determine its activity with different cell lines (Farias et al., 2019).

Taxol (Paclitaxel)

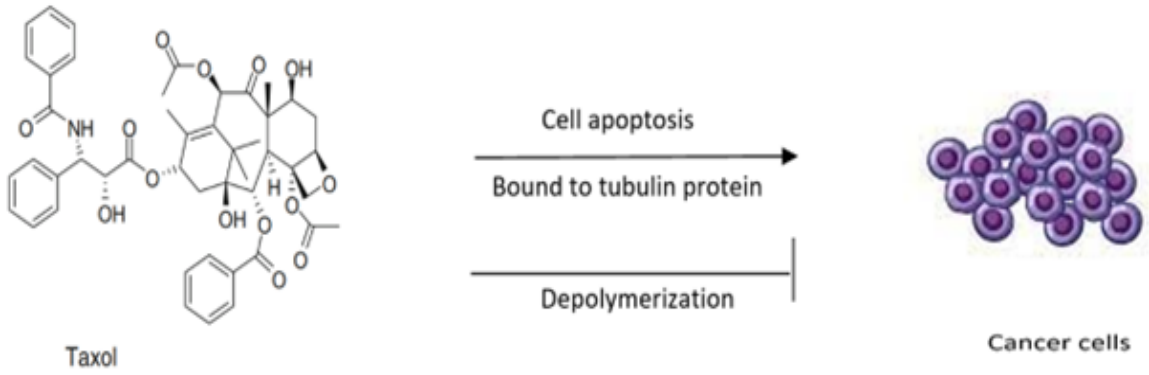
Taxol was obtained from the bark of *Taxus brevifolia* for the first time, which is a potential bioactive compound marketed under name Taxol (Wani et al., 1971). Other than *Taxus brevifolia* several other species of taxus like *Taxus canadensis, Taxus baccata, Taxus wallichiana, T. cuspidata, T. sumatrana, T. floridana, T. chinensis, T. yunannensis* and *T. mairei* also produce taxol (Majumder and Jha 2009). Researchers analysed the presence of natural bioactive compounds in Taxol during early 1960s and later it turned out as the world's first billion-dollar anticancer drug, belonging to the class of taxanes that is highly functionalized polycyclic diterpenoid. Submerged culture methods are also used for the production of paclitaxel (Zaiyou et al., 2017). Paclitaxel isolation and identification in its pure form from the extracts takes several years and after all these tedious procedures it is identified as a potent antitumor source (Uzma et al., 2018). Submerged culture methods are also used for the production of paclitaxel (Zaiyou et al., 2017). When a culture fermentation supplemented with certain useful substances such as precursors, carbon sources, metabolic bypass inhibitors, inducers, and nitrogen sources along with an optimized culture parameter, will provide an increased concentration of paclitaxel from the fungal endophytes (Zhao et al., 2016)

The plant from which Taxol was extracted was not abundant in nature (Cragg et al., 1993). To meet the market requirements of a continuously growing market, semi-synthesis industrial production of taxol was not adequate (Ji et al., 2006). Since only a limited amount of Taxol is obtained from the bark (0.01–0.05 %) (Wheeler et al., 1992). Without causing any damage to the plants, Baccatin III and 10-deacetylbaccatin III like late precursors of Taxol can be isolated from the needles of yew trees and using synthesized side chain molecules they can be used to produce desired products (Strobel et al., 2004). About an 8-fold increase in taxol production was obtained by using the method of induced production, through which fungal endophyte *Periconia sp*. associated with *Torreya grandifolia* were induced for Taxol production and that has been demonstrated in a report through the application of benzoic acid. Here the fungal metabolism is activated by benzoic acid, which acts as an activator (Li et al., 1998). For the enhanced Taxol production several parameters are used and optimised since the Taxol production from endophytic fungi was not stable and that caused a decline in the production of Taxol after several generations (Venugopalan et al., 2015; Qiao et al., 2017). About 10 tons of bark equal to almost 300 trees are required for Taxol extraction in need of 500 patients diagnosed with cancer (Wheeler et al 1992). Large-scale independent production of paclitaxel was demonstrated by a group of researchers during the genome sequence analysis of *Penicillium aurantiogriseum* NRRL 62,43, a fungal endophyte (Yang et al., 2014).

Usually, paclitaxel action involves the binding of paclitaxel with the tubulin protein of the mitotic spindle and makes them non-functional. That causes the arrest of mitosis in the M phase due to the stabilization of microtubules causing the cell cycle reversal to the G0 phase which results in apoptosis (Brito et al., 2008). The paclitaxel can be used either alone or in combination with other anticancer therapy for the treatment of cancers like non-small lung cancer (NSCLC), ovarian cancer, breast cancer, AIDS-related Kaposi sarcoma and AIDS-related Kaposi sarcoma. This was approved by the (FDA) Food and Drug Administration (Krown et al., 2020). Among 4 different endophytic fungi from the bark of *Taxus baccata*, Stemphylium sp. The fungal strain was observed for the production of Taxol (Zaiyou et al., 2017). During the early 1990's the structure of paclitaxel was clinically introduced to the US market but the structure was elucidated in the year of 1971 (Rowinsky et al., 1992). The US FDA approved Taxol (paclitaxel) for treating ovarian cancer in 1992, that is two decades after its discovery and its sales reached almost $3 billion in 2004 (Wani and Horwitz 2014). Baccatin III is one of the late precursors of Taxol, some species like *T.baccata* produce Taxol in smaller amounts and only late precursors for up to an adequate amount. While considering the overall taxoid content Taxol accounts for only a smaller proportion (Nadeem et al., 2002). Taxol prevents depolymerization of microtubules by promoting the stability of polymerization, these are the unique properties of taxol that lead it to act as an antineoplastic agent (Kumar et al., 2021). There are several species of endophytic genera that are conformed for the production of Taxol which includes, *Botryodiplodia theobromae, Periconia sp., Bartalinia robillardoides, Alternaria alternata, Pithomyces sp., Monochaetia sp., Seimatoantlerium nepalense* and *Chaetomella raphiger* (Kumar et al., 2017).

Paclitaxel shows anticancer activity by targeting the mitochondria, apoptotic inhibitor proteins such as B-cell Leukemia 2 (Bcl-2) and immune cells, other than the cell cycle arrest (Ferlini, et al., 2003) Angiogenesis is an important feature of cancer cells. According to previous studies, decreasing the expression level of Bcl-2 and increasing the expression levels of DR5 and cleaved caspase-3 paclitaxel enhances the effect of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) in metastatic cervical cancer (Sun et al., 2018). Taxol used as a drug against cancer cells has been extensively tested and examined for its antiangiogenesis properties (Lau et al., 1999). The expression of vascular endothelial growth factor (VEGF) in the murine Met-1 strain was suppressed by paclitaxel. That was the first evidence obtained for the cell inhibition of angiogenesis in VEGF

tumours (Lissoni et al., 2000).Several methods like spectroscopic (Matrix-assisted laser desorption/ionization—Time of flight [MALDI-TOF], Fast atom bombardment, immunological techniques (using monoclonal antibodies specific for paclitaxel, Thin layer chromatography, High-performance liquid chromatography and Nuclear magnetic resonance [NMR] are used to detect paclitaxel from endophytes extracts (Flores Bustamante et al., 2010).



Fig; 1

Podophyllotoxin

Podophyllotoxin belongs to the chemical group of lignans. They are pharmaceutically active natural drugs, used as precursors of antitumor drug synthesis. Some of the important antitumour drugs like etoposide (VP-16-213) and teniposide (VM-26) uses podophyllotoxin as their precursor molecule, those drugs are used in the treatment of testicular cancer, lung cancer, and other solid tumour and a variety of leukaemias (Majumder and Jha 2009). Podophyllotoxin is structurally related to Etoposide and its thiophene analogue teniposide (Patel et al., 2010). Due to the cytotoxic potential of podophyllotoxin and its analogues, they are pharmacologically very important (Ardalani et al., 2017). Other than the anticancer property, they are also effectively used against microbial infections, immunological disorders, viral diseases and oxidative stress. To avoid the toxic side effects of direct podophyllotoxin usage, its semisynthetic derivatives like Etoposide, Etopophos and Teniposide were used as cytotoxic drugs.

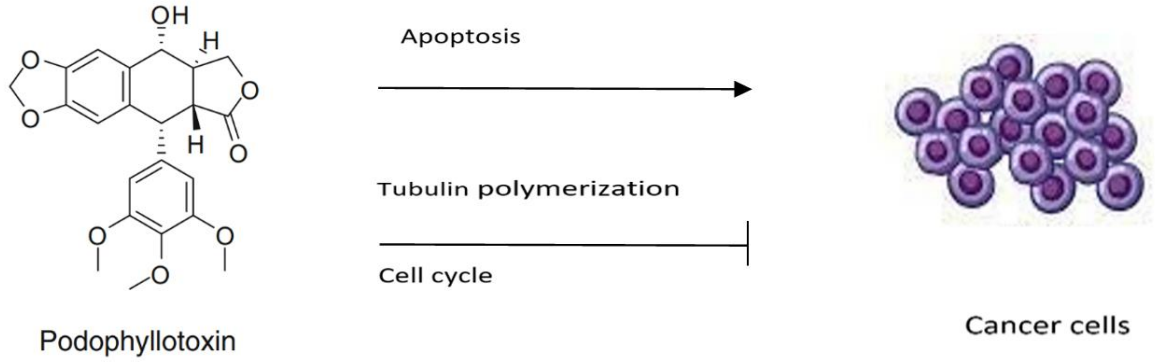
Due to low yield, they are not economically feasible, however in the past several years lots of efforts were made for the better production of podophyllotoxin from different plant species (Chandra, 2012). Dysosma, Sinopodophyllum (also called Podophyllum), Diphylleia and Juniperus are some of the genera they widely distributed (Li et al., 2013). Another two examples of podophyllotoxin-producing fungi are *Chaetomium globosum* strain MF564 and *Pseudallescheria* sp. T55 of Ascomycota division (Wang et al., 2017). However, because of the low abundance of plants that produce podophyllotoxin, the supply of their derivatives from traditional sources was also limited. For the improved production of podophyllotoxin-related compounds, plant tissue culture-like alternative strategies were used as alternate, sustainable and reliable strategies for the production of plant-origin natural compounds (Ochoa-Villarreal et al., 2016). *Fusarium* strain WB5121 associated with *Dysosma versipellis* was reported for the isolation of pododphyllotoxin with the highest yield of 277 µg/g of dry-weight mycelia (Tan et al., 2017). Fungal endophytes such as *Juniperus communis* L. *Trametes hirsuta*, Horstmann, and *Phialocephala fortinii* isolated from plants *Juniperus recurve* and *Podophyllum peltatum*with anticancer properties act as the source of podophyllotoxin (Ardalani et al., 2017). Podophyllotoxin was produced at a large scale that is, about 28.8 µg/g of the dry mass of mycelia by fungal strain JRE1 *Fusarium oxysporum*, from *Juniprerus recurva* (Kour et al., 2008).

Angiosperms as well as gymnosperm plants produce podophyllotoxin with anticancer properties, they are popular aryl tetralin lignan (Majumder and Jha 2009). Over the last two decades for cancer treatment, the etoposide derivative has been widely used. The endophytic fungus *Fusarium solani* produces podophyllotoxin that IS isolated from the root of *Podophyllum hexandrum and* acts as a source. 189 µg/L podophyllotoxin was obtained from the fungal endophyte *Phialocephala fortinii* isolated from *Podophyllum peltatum.* Another report in support of this describes a strain of *Fusarium solani* yielding 29.0 µg/g Podophyllotoxin (Nadeem et al., 2012). *Alternaria tenuissima* is a podophyllotoxin-producing endophyte seen in association with the root of *Sinopodophyllum emodi* L (Liang et al., 2016). *The* Discovery of the process of production of secondary metabolites by fungal endophytes was a tremendous lead in the biological and commercial sector. Fungal culture can be scaled up for the adequate production of desired metabolite in need of new drug development without the load of harvesting wild population from natural habitat (Eyberger et al., 2006). Fluorescence-activated cell sorting (FACS) analysis revealed that the carbamate derivative of pododphyllotoxin called 4′-O-demethyl-4β-[(4-

hydroxymethyl)-1,2,3-triazol-1-yl]-4-desoxypodophyllotoxin cyclopentyl can induce cell cycle arrest at G2/M phase, apoptosis, inhibits microtubule formation, and inhibits DNA topoisomerase II. Some other promising cytotoxic activities are shown by the carbamate derivative 4β-(1,2,3- triazol-1-yl) podophyllotoxin against cancer lines, human colon carcinoma cells (HCT-8), HeLa cells, human lung adenocarcinoma cells (A549) and human promyelocytic leukaemia cells (HL-60) (Liu et al., 2020). Podophyllum (Berberidaceae) plant resins historically act as the source for the isolation of podophyllotoxin. The species *podophyllum emodi* L. and *Podophyllum peltatum* L., are commercially the most exploited species under this genus (Newman and Cragg 2020; 2. Feher and Schmidt 2003). The antitumor property of Etoposide and teniposide was due to their interaction with topoisomerase II enzyme (Cortés and Pastor, 2003). Fungal endophyte *Alternaria tenuissima* isolated from the fresh roots of *Sinopodophyllum emodi*(Wall.) Ying at Xinglong Mountains, Gansu Province, China was known to produce podophyllotoxin, identified when the secondary metabolite analysis of fungal biomass (Liang et al., 2016). Certain plants are able to produce podophyllotoxin-related compounds such as podophyllotoxin glucoside and dimethoxy podophyllotoxin. *Trametes hirsuta* associated with the rhizome of the *Podophyllum hexandrum* is one of the best examples of this. In the case of fungal endophyte *Trametes hirsute* podophyllotoxin production initiated at 72h while declined rapidly after 96h (Puri et al., 2006).

There are two mechanisms by which topoisomerase inhibitors impart their function one is by the elimination of catalytic activity and the second one is by increasing the levels of topoisomerase II: DNA covalent complexes (often designated as topoisomerase II poisons) (Nitiss, 2009). The antimitotic activity of

Fig; 2



podophyllotoxin affects the cells by preventing tubulin polymerization, which will induce the arrest of the cell cycle at the stage of mitosis and the formation of mitotic spindle microtubules. Alkaloids and colchicines show a very similar mechanism of action as the antimitotic activity of podophyllotoxin (Passarella et al., 2010). As a result of its action, the cell cycle arrest in the early metaphase stage causes the death of epithelial cells. Accumulation of mitosis-related proteins BIRC5 and aurora B leads to mitotic arrest by preventing microtubule polymerization (Chen et al 2013). Mitotic arrest due to the imbalance between the assembly and disassembly of microtubules created as a result of podophyllotoxin, and tubulin binding (Guerram et al., 2012). In cancer cells, it initiates a pro-apoptotic endoplasmic reticulum stress signalling pathway. Growth of tumour cells was inhibited by intraperitoneally injected 2mg/kg of podophyllotoxin and also showed a paclitaxel similar antineoplastic activity (Wrasidlo et al., 2002). Podophyllotoxin shows antineoplastic activity against metastatic lung cancer (Utsugi et al., 1996). They induce apoptosis by inhibiting the tubulin assembly into microtubules (Abad et al., 2012). Epidophyllotoxin is an active antitumor agent and isomer of podophyllotoxin, which was isolated from the roots of podophyllum species, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich (Berberidaceae) (Stahelin, 1973)

Camptothecin

Camptothecin is a water-insoluble compound. Which is used as an important anticancer agent in cancer medication and is commonly obtained from plants. The compound is currently approved against cancer and acts as a promising anticancer agent, a potent antineoplastic agent. It is a pentacyclic pyrroloquinoline alkaloid used in the anticancer drug preparation, in the form of irinotecan and topotecan. Mostly camptothecin was isolated from *Camptotheca acuminata* and *Nothapodytes foetida* and it is the third largest drug that is used in cancer treatment (Demain and Vaishnav 2011). In several endophytes to achieve the maximum production of bio-active phytochemicals different parameters like mathematical designs [response surface methodology (RSM) and artificial neural network (ANN)], bio-reactor optimizations, metabolic engineering strategies etc. were used. In

the last few years, one or more response variables in medicinal plants were optimized successfully by RSM (Rahman et al., 2019; Kaur et al., 2019). The crucial step in the screening of fungal endophytes is the selection of culture media. Potato dextrose medium (PDA/ PDB) is the most common media for growing fungal isolates from CPT-producing plants (Musavi et al., 2015; Venugopalan et al., 2016).

At first campothecin (a potent anticancer quinoline indole alkaloid) was isolated from the bark of *Camptotheca acuminata* in 1966 but it was also obtained from some other plants including *Miquelia dentata*, *Nothapodytes nimmoniana*, and Ophiorrhiza (Wall and Wani 1996). Monoterpenoid indole alkaloids are formed from seco-iridoid and an indole moiety through several enzymatic steps in the later stage of their synthesis, they are bioactive compounds belonging to multistep biosynthetic pathways (Rather et al., 2017). They specifically target the intranuclear enzyme DNA topoisomerase I (Topo 1), which is needed throughout DNA replication and transcription to swivel and relax DNA, that is their action mechanism involves eukaryotic DNA (Wani et al., 1971). According to numerous studies, it was clear that Topoisomerase 1 enzyme concentration was higher in cancer cells when compared with normal cells and also this enzyme has a significant role in cancer cell replication machinery (Dancey and Eisenhauer 1996). The interaction between camptothecin and its derivatives with the enzyme topoisomerase 1 cleavage complex results in the stabilization of the enzyme and then the initiation of an apoptotic event series that will finally lead to the death of the cell (Raveendran 2015). These alkaloids target only topoisomerase I apparently like this property camptothecin and their derivatives are unique for a number of reasons. In the case of yeast cells that lacked Topoisomerase I, they were immune to the cytotoxic effects of CPT (Bjornsti et al., 1989). Two enantiomeric forms of Camptothecin present in nature are 20-S camptothecin and 20-R camptothecin (Uzma et al., 2018). Camptothecin inhibits topoisomerase I by blocking the re-joining stage of topo-1 cleavage which results in the formation of an intermediate covalent reaction and forms the cleavable complex. By potential lethal collisions between progressing replication forks and cleavable topo-I complexes they primarily kill cells in the S-phase and the cytotoxicity of CPT resulted from the formation of long-lived lived topo-I DNA complexes by the collisions with the transcription machinery (Liu et al., 2000).

Around 600kg of camptothecin is produced a year worldwide but about 3000kg/year is the total demand for camptothecin on the international market, so the pharmaceutical industry in the manufacture of anticancer drugs cannot satisfy this requirement (Takimoto et al., 2002). There are several investigations ongoing for developing novel methodologies and approaches for the production of camptothecin from different endophytic fungi. *Nothapodytes foetida* inner bark inhabiting fungus Entrophospora *infrequens*, was grown for maximum production of camptothecin in an optimised condition with different nutrient combinations either alone or in the combination of different nitrogen and carbon sources (Amna et al., 2006). Two camptothecins, topotecan (fig; 1) and irinotecan (fig; 2) were approved by FDA for the treatment of colorectal cancer, small-cell lung cancer, and ovarian cancer almost four decades after the identification of C. acuminata extract's antitumor activity (Blagosklonny 2004).

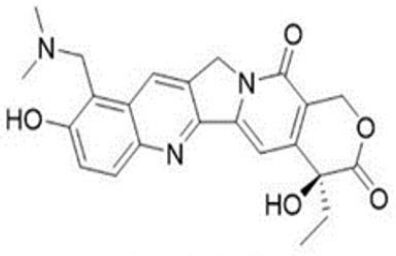


Figure 1: Topotecan

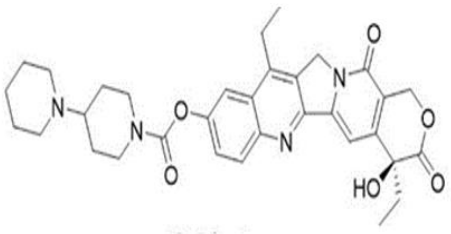


Figure 2: Irinotecan

Fig; 3

Other than *Camptotheca acuminata* another seven families produce camptothecin they are Betulaceae (*Alnus nepalensis*), Gelsemiaceae (Mostueabrunonis), Rubiaceae (*Ophiorrhiza alata, Ixora coccinea*), Piperaceae (*Piper betel*), Meliaceae (*Dysoxylum binectariferum*), Apocynaceae (*Ervatamia heyneana* and *Chonemorpha fragrans*) and Violaceae (*Rinorea anguifera*) (Zhang et al., 2019). Endophytic bacterium *Paenibacillus polymyxa* (LY214) isolated from *Camptotheca acuminata* yielded .8 mg/l CPT in 2nd generation which declined constantly up to 0.8 mg/l at the 8th generation (Pu et al., 2015). Recently lessening of the compound's natural sources due to low yield has emerged in Asia, since because of the increased demand for camptothecin resulted in enormous harvesting of the trees producing it (Nadeem et al., 2012). Therefore, there occurs an urgent need to

find out an effective reliable alternative method and other plant sources for the consistent supply of essential compounds such as camptothecin is required. According to the studies, the fungus *Entrophospora infrequens* from the *Nothapodytes nimmoniana* plant as a major source of camptothecin production. In endophyte *Trichoderma atroviride* containing camptothecin a yield attenuation was observed (Nadeem et al., 2012). Camptothecin production scaling up using endophytes was the main challenge that existed in yield amplification (Clarance et al., 2019). *Alternaria alternata, Fomitopsis sp.,* and *Phomopsis sp.* three fungal species also act as the prominent CPT producers (Shweta et al.,2013). *Entrophospora infrequens*, endophytic fungi isolated from the inner bark tissue of *Nothapodytes foetida* yields camptothecin of 18 µg/mg of dry weight mycelia from the choloroform extract. Cytotoxic activity against human ovarian cancer cells (OVCAR-5), liver cancer cell (HEp2), and lung cancer cells (A549) were shown by Camptothecin isolated from Entrophospora *infrequens* (Puri et al., 2005). Camptothecin is also isolated from Endophytic fungus *F. solani* from *Apodytes dimidiate* in the western ghats (Shweta et al., 2010).

The two limiting factors for the application of Camptothecin as an anticancer agent are inadequate water solubility and high toxicity. To overcome this side effects two derivatives of camptothecin known as 10-hydroxycamptothecin (HCPT), and 9-methoxycamptothecin (MCPT) were used with the same medicinal efficacy and without the above limitations (Kusar et al., 2009). From woody climber *Pyrenacantha volubilis* four strains of bacillus bacterial endophytes were isolated. Among the four studied only *Bacillus subtilis* strain (KY741853) produced maximum CPT yield (0.106 mg/g) and CPT yield decreased significantly from 0.18 mg/g to 0.03 mg/g in sub-culturing (up to 5th sub-culture generation) (Soujanya et al., 2017). Several camptothecin derivatives have been identified as good anticancer agents for example rubitecan (9-nitrocamptothecin), 10,11-methylenedioxy camptothecin and IDEC-132 (9-aminocamptothecin) (Ulukan and Swaan, 2002). Strictosidine catalyzed by the enzyme strictosidine synthase and resulted in the formation of secologanin and tryptamine and their compressed product is the CPT. In recent years few studies are pointed out the candidate genes for CPT production and key enzymes encoding their regulation in some plants such as *Ophiorrhiza pumila* (Rubiaceae), *Camptotheca acuminata* (Nyssaceae) and *Nothapodytes nimmoniana* (Icacinaceae) plants (Manjunatha et al., 2016; Rather et al., 2017).

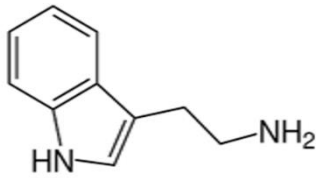


Figure: Tryptamine

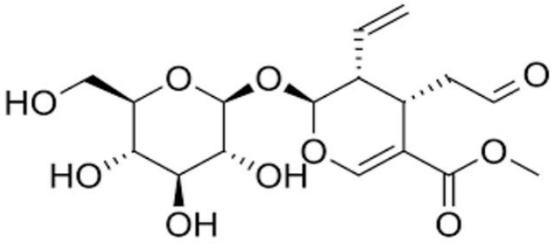
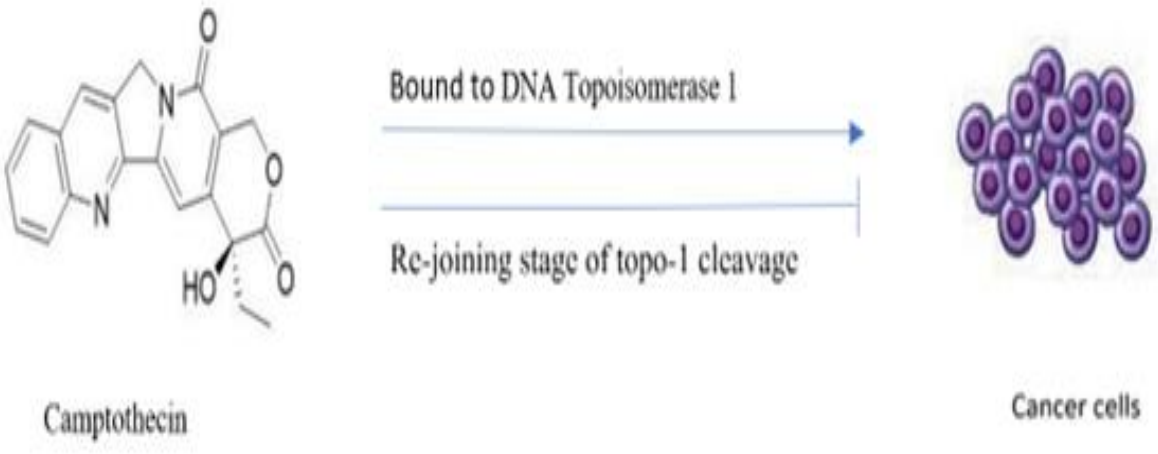


Figure: Secologanin

Fig; 4

16 strains among ninety-four endophytic fungi isolated from *Camptotheca accuminata* displayed cytotoxicity to Vero or PC3 cells. *Fusarium solani*, endophytic fungi demonstrated maximum cytotoxic activity against the cancer cell and camptothecin was found to be generated through TLC, HPLC and EI-MS analysis (Ran et al., 2017). Using high-performance liquid chromatography, it was detected that *Aspergillus niger* also produces camptothecin and it was isolated from *Piper betel*. Cytotoxic activity in the colon cancer cell line was also detected (Aswini and Soundhari 2018). The highest yield of CPT (146 mg/l) with mixed fungal (FI + F2) cultures was observed when comprehensively optimising the significant fungal culture parameters and experimentally, these results were compared with the monocultures of *Colletotrichum fructicola* F1 (33 mg/l) and *Corynespora cassiicola*-F2 (69 mg/l). *Fusarium oxysporum* isolated from the same plant viz. *Nothapodytes nimmoniana* monoculture individually yielded a large amount of CPT (90 mg/l) (Bhalkar et al., 2016). Development of camptothecin was again detected from endophytic fungi isolated from the bark of *Camptotheca acuminata* (Kusari et al., 2009). Aspergillus sp. LY341, Aspergillus sp. LY355, and *Trichoderma atroviride*LY357 are three camptothecin producing fungi isolated from *C. acuminata* their yields were 7.93, 42.92, and 197.82 µg/L, respectively. With repetitive subculture unfortunately strains LY341 and LY355 lost the camptothecin-producing capability. But from second to eighth generation consistent production of camptothecin was observed in strain LY357 (Kai et al., 2015). *Fusarium nematophilum* (XSXY09), *Alternaria alternate* (XSQZ04) and *Phomopsis vaccinii* (XSCY02), are three fungal strains obtained from Camptotheca acuminata were tested in submerged culture condition for CPT production (Su et al., 2014). 37 mg/g, 29 mg/g and 24 mg/g CPT were produced by these three fungal strains viz. XSXY09, XSQZ04 and XSCY02 respectively (Soujanya et al., 2017). 0.175 mg/l CPT was produced by the fungal strain *Aspergillus niger* isolated from *Piper betel* (Aswini

and Soundhari 2018). According to a new study among 94 strains isolated from *Camptotheca acuminata* only one fungal strain (S-019) viz. *Fusarium solani* (commonly belonging to genera: *Alternaria* sp. *Cephalosporium* sp., *Pestalotiopsi* sp. and *M* sp.) following 96 h of incubation resulted in the production of CPT (40 § 5 mg/g) (Ran et al., 2017).



Fig; 5

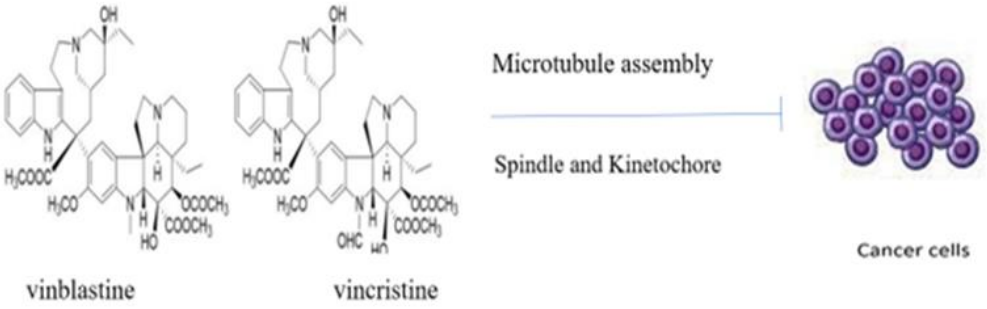
Vinca alkaloids

Leaves of vinca plants are the natural source of bioactive compounds. The leaves of vinca plants have long been used to treat various diseases. Researchers have reported that it also has hypoglycemic, hypotensive and purgative properties. But the growth rate of these plants is very low and a huge number of leaves will be required for extraction. In the 1950s two research teams discovered the antitumor properties of the plant. Vinblastine and vincristine are the two natural vinca alkaloids obtained from *Catharanthus roseus* or Vinca rosea and are used in the treatment of lymphoma and leukaemia, respectively (Barnett et al., 1978). Vinca alkaloid isolation story was known during the late 1950s, and it was first isolated from Madagascar periwinkle (the botanical name is *Catharanthus roseus* G. Don and commonly called Vinca rosea). According to Jamaican folklore, in the absence of insulin, the extracts of periwinkle were used as an oral hypoglycemic agent (Noble, 1990). *C. roseus* leaf extracts were identified as the treatment for diabetes, which had a strong effect on bone marrow and white blood cells. Vincaleukoblastine was the compound that was isolated ultimately from the leaf and later it was changed to vinblastine (Noble et al., 1958). Vinca alkaloid compounds inhibit cell proliferation by binding to microtubules. Beta tubulin polymerization was prevented by vincristine and its derivatives by binding to it. To alter the function of protein kinase the cell association with vinca alkaloids induces the p53 tumour protein and the 1a (p21) CDK (cyclin-dependent kinase). Thus, the Bcl2 was phosphorylated and inhibited by this protein kinase. The ability of Bcl2 to form a heterodimer with BAX is lost due to the phosphorylation by protein kinase and functions of Bcl2 will be impaired due to increased activity of p53 and p21 finally all this may together trigger apoptosis. The poor expanding ability of the mitotic spindle due to contact with vinca alkaloids contributes to the apoptosis of the cell (Drukman and Kavallaris 2002). According to some reports Quercetin, an epigenetic modifier has the ability to induce the production of vinblastine in the endophytic fungi *Penicillium concavoradulozum* VE89L and *Aspergillus amstelodami* VR177L derived from vinca plants (Gulyamova et al., 2019). Previous reports have shown that vinblastine from vinca plants exhibits cytotoxic activity against cancer (Thirumaran et al., 2007). This compound was used in the treatments of Leukemias, lymphomas, and testicular cancers (Retna and Ethalsa 2013).

Vinblastine and vincristine serve as inhibitors during the metaphase of the cell cycle and they inhibit the progression of the mitotic spindle by binding to the microtubule (Kumar 2016). The principal action of vincristine is interference with the arrangement of microtubules and mitotic spindle dynamics, disturbance of intracellular transport and decreased blood flow of tumours, the latter likely due to anti-angiogenesis (Zhao et al., 2010). In the treatment of various malignancies, vinca alkaloids represent the second most used class of anticancer drugs Coupling of catharanthine monomer and vindoline resulted in the formation of terpenoid indoles vinca alkaloids, and they are used in chemotherapy due to their ability to reduce the number of white blood cells in acute lymphoblastic leukaemia and nephroblastoma (Moudi et al., 2013). Anticancer alkaloids including vinblastine, vincristine, vinleunosine, and vinrosidine were discovered through the thorough phytochemical investigation of the extract over a period of a decade (Johnson et al., 1963; Noble 1990; Noble 2016). The first report about the case of vinblastine production by endophytic fungi is the Alternaria sp. isolated from the phloem of *Catharanthus roseus* vinblastine (Haiyan and Lingqi 1998). Production of high-yield vinblastine i.e., 182 μg/L for the first time

produced by the endophytic fungi *Curvularia verruca – losa* in abundance compared to other fungi was reported for the first time (Parthasarathy et al., 2020)

Alternaria sp. of endophytic fungi produce vinblastine (Guo and Zhang 1998) and *Fusarium oxysporum* sp. have the ability to produce vinblastine (Zhang et al., 2000), both of these fungal strains are isolated from *Catharanthus roseus. The production* cost of vinblastine and vincristine is very high due to very low productivity in plants (0.001–0.0003%). As a reliable method to save plants from extinction and to reduce the cost of these drugs, fungal endophytes were considered as an alternative method (Kumar 2016). Vincristine and vinblastine are used as approved drugs for the treatment of Hodgkin lymphoma. Along with those structural analogues of vinca alkaloids (Vinflunine, Vinorelbine, Anhydrovinblastine) targeting tubulin polymerization are in phase-II/III trials for the treatment of breast cancer and carcinoma (Kaur et al., 2014). *Nigrospora sphaerica* fungal endophyte isolated from Catharanthus roseus showed the presence of vinblastine and was later tested against the breast cancer cell lines MDA-MB 231 (Ayob et al., 2017). The yield of dimeric alkaloids was very poor. Growing *Catharanthus roseus* in the field was much more economical since it is difficult to culture shoots in a bioreactor (Wink M et al., 2005). semi and complete synthesis technique of tissue and shoot culture, miracle drugs, vincristine and vinblastine isolated from the leaves of *Catharanthus roseus*. Since the sources are inadequate and unable to face current needs without exploitation, these methods allow access to the medication. To provide the patient with medicine at an affordable rate and through the same instinct taking time into account nature conservation obligations, and using various fungal endophytes from *Catharanthus roseus* as the source (Kumar et al., 2013). *Talaromyces radicus* endophytic fungi from *C. roseus* contained 670 µg/L of vincristine and 70 µg/L of vinblastine. Partially purified vincristine was tested for cytotoxicity in HeLa, MCF7, A549, U251, and A431 cells. Dose-dependent growth inhibition in HeLa, MCF7, A549, U251 and A431 with IC50 values of 4.2, 4.5, 5.5, 5.5 and 5.8µg/mL, respectively was observed as the cure of vincristine. However significant impacts were not observed on normal cells HEK293 (Palem et al., 2016; Song et al., 2016).



Fig; 6

Piperine

Piperine is found in the fruits of *Piper nigrum* L (black pepper*)* and *Piper longum* L (long pepper) which is responsible for the pungent taste of those fruits. It has anti-inflammatory and anticancer properties. It is a potent anticancer alkaloid (Zheng et al., 2016). The mechanism of action of piperine as a chemopreventive mechanism includes inhibition of cell proliferation, activation of apoptotic signalling cascades, modulation of autophagy, and inhibition of cell cycle and angiogenesis. Piperine has antidiabetic properties in which it enhances the hepatic-oxidized glutathione and decreases renal glutathione concentration and renal glutathione reductase activity (Manayi et al., 2019). Piperine also inhibits lipopolysaccharide-induced expression of interferon regulatory factor, decreases the liver marker enzyme activity, reduces the activation of STAT1, and inhibits the release of Th-2-mediated cytokines indicating its anti-inflammatory activity. Anticancer activity expressed by piperine through following ways activates caspase-3 and caspase-9, cleaves poly(ADPribose) polymerase (PARP), decreases Bcl-2 protein expression and increases Bax protein, reduces the expression of phosphorylated STAT3 and nuclear factor kappa B (NF-kB) transcription factors, blocks extracellular signal-regulated kinase (ERK1/2), p38 MAPK, and AKT signalling pathways, and suppresses epidermal growth factor (EGF)-induced matrix metalloproteinase (MMP)-9 expression (Stojanovi et al., 2019).

Through the suppression of the MMP-9 expression and MMP-13 inhibition of PKCα and ERK phosphorylation and reduction of NF-κβ and AP-1 activation, antitumor anti-invasive effects of piperine have been explained (Hwang et al., 2011). Recent reports explain that piperine shows phosphoinositide-3 kinase (PI3K)/Akt signalling mediated inhibition of angiogenesis in human umbilical vein endothelial cells (HUVECs)

(Doucette et al., 2013: Karar and Maity 2011). Towards certain drugs and nutrients, it has the bioavailability-enhancing ability. The cultures of endophytic fungal species such as *Periconia* sp., C. *gloeosporioides*, and *Mycosphaerella* sp. isolated from *Piper* spp act as a source for the extraction of piperine (Chithra et al., 2014; Verma et al., 2011). Recently *Phomopsis* sp. from *Oryza sativa* has also been reported as a source for isolation of piperine (Chithra et al., 2017). Through the induction of autophagy piperine exhibits inhibition towards prostate cancer cells (LNCaP and PC3) and also it inhibits mTORC1 activity in Caco-2 and HT-29 cells (Yun et al., 2013). In TRIAL (tumour necrosis factor-related apoptosis-inducing ligand) based therapy piperine is used as the adjuvant that mediates apoptosis in TRAIL-sensitive and TRAIL-resistant triple-negative breast cancer (TNBC) cells by inhibiting survivin and p65 phosphorylation (Abdelhamed et al., 2014; Mérino et al., 2007). By down-regulating the Wnt/b-catenin signalling pathway and modifying the self-renewal properties of cancer stem cells (CSCs) piperine inhibits the CSCs (Kim et al., 2012; Li et al 2011).

Pyrans and Pyrones

Pyran is one of the most significant non-aromatic structures found in nature. Which contains a six-membered ring composed of one oxygen and five carbon atoms. Pyran and its derivatives show a wide range of bioactivities, most importantly they show anti-cancer properties (Grover et al., 2022). 5-butyl-6-(hydroxymethyl)-4- methoxy-2H-pyran-2-one and 4-methoxy-6-methyl-5- (3- oxobutyl) -2H-pyran-2-one are two novel pyrans obtained from *Alternaria phragmospora*, an endophytic fungus from Vinca rosea leaves displayed moderate antileukemic activities against HL60 cells (IC50 values of 2.2 and 0.9 μM) and K562 cells (IC50 values of 4.5 and 1.5 μM) (Metwaly et al., 2014). Fungal endophyte *Nodulisporium* sp. isolate from the stem of Aquilaria sinensis the presence of a novel benzopyran, (2R*, 4R*)-3,4-dihydro 4-methoxy-2- methyl-2H-1-benzopyran-5-ol. It shows relatively a mild cytotoxicity towards the cell line SF-268 having 100 mg/ml concentration as compared to cisplatin (positive control) (Wu et al., 2010)

The α-Pyrones are one of the most important structural features found in a huge variety of biologically active metabolites. During in vitro analysis of cytotoxic inhibition upon the application of naphtha-gamma pyrone, TMC 256 A1, Cytotoxic inhibitions against cancer cells of MCF-7, Hep3B, SNB19, MDA-MB-435, Huh7 and U87 MG (IC50 19.92– 47.98 μM) were observed (Chen et al., 2016). Genus Aspergillus of fungal endophyte acts as the major source of the metabolites of pyrones and its derivatives (Liu et al., 2011). Nigerapyrone B is the derivative of α-Pyrone isolated from the endophytic fungus *Aspergillus niger* MA132 from the inner tissue of marine mangrove plant *Avicennia marina*. Selective activity against the HepG2 cell line with an IC50 of 62 μM was shown by Nigerapyrone B. The positive control, fluorouracil showed cytotoxicity against tumor cell lines A549, HepG2, DU145, MCF-7, SW1990, NCI-H460 and MDA-MB-231, with IC50 values of 52, 109, 3.3, 31, 121, 8.5 and 59 μM respectively (Huang et al., 2011).

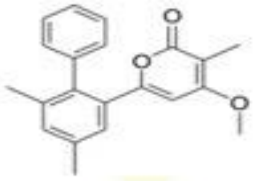


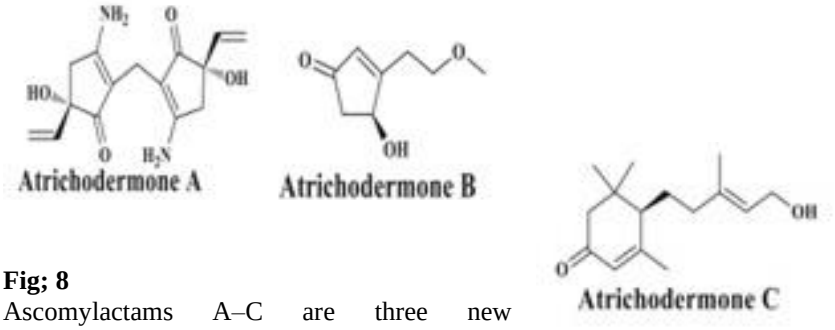
Figure: Nigerapyrones B

Fig; 7

Alkaloids

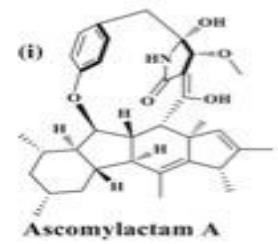
Alkaloids are nitrogen-containing compounds with low molecular weight, pharmaceutically very significant due to their high biological activities. They are mostly derived from amines, which are produced by the decarboxylation of amino acids, such as histidine, lysine, ornithine, tryptophan and tyrosine. They are naturally occurring compounds, with therapeutic uses such as antitumor, antimicrobial, anti-hyperglycemic, anti-asthmatic vasodilatory and antimalarial agents (Keshri et al.,2021). The biological properties shown by alkaloids derived from plants include many bioactivities of toxicity, medicinal properties and recreational purposes. Studies have been conducted on various alkaloids obtained from plants for their use as potential agents against cancer and many of them are isolated from fungal endophytes also. (Kharwar et al., 2011). Diverse biological activities like anti-viral, anti-fungal and anti-cancer properties are carried out by alkaloids as the secondary metabolites produced by endophytic fungi (Silva et al., 2007). An endophytic fungus *Hypomontagnella monticulos* Zg15SU isolated from *Zingiber grifthii* yielded a novel terpenoid–alkaloid skeleton-based compound, called griffithiiene with strong potential against pancreatic, bladder and Colon cancer cell lines (Panc-1, NBT-T2, and HCT116) with IC50 values in the range of 0.05–0.75 ppm (Lutfa et al., 2021). Ascomylactams A–C are three new alkaloids extracted from the Didymella sp. fungal endophyte of mangrove plant. Among them ascomylactam A shows maximum

cytotoxic activity against the NCI-H460 human cancer cell line with an IC50 value of 4.4 μM (Chen et al., 2019). Crinine-type alkaloids possess anticancer activities (Evidente and Kornienko 2009). Aulicine and 3-O-methyl-epimaco wine are examples of crinine-type alkaloids that are isolated from *Hippeastrum calyptratum* Herb. and *Hippeastrum aulicum* Herb. (Andrade et al., 2014). The biological properties shown by alkaloids derived from plants include many bioactivities of toxicity, medicinal properties and recreational purposes. Studies have been conducted on various alkaloids obtained from plants for their use as potential agents against cancer and many of them are isolated from fungal endophytes also. (Kharwar et al., 2011). A new alkaloid compound GKK1032C, extracted from the endophytic fungus Penicillium sp. CPCC 400817, associated with mangrove plants. About 1.6 μg/mL MIC value of antibacterial activity exhibited by GKK1032C against the bacterium *Staphylococcus aureus* (Qi et al., 2019). Three novel compounds Atrichodermones A, B, and C isolated from endophytic *Trichoderma atroviride*, shows cytotoxic activity against U967 and HL60 cell lines and anti-inflammatory effect against IL-1β and TNF-α (Zhou et al., 2017).



Fig; 8

Ascomylactams A–C are three new macrocyvclic alkaloids extracted from *Didymella* sp. fungal endophyte of mangrove plant. Ascomylactams A shows maximum cytotoxic activity against the NCI-H460 human cancer cell line with an IC50 value of 4.4 μM (Chen et al., 2019).



Fig; 9

Chaetomugilide, a novel alkaloid isolated from the fungus *Chaetomium globosum* TY1 inhabiting the bark of *Ginko biloba* shows cytotoxicity against human hepatoblastoma HepG2 (Yuan et al., 2019). Chaetomugilide A shows a substantial degree of cytotoxicity against HepG2 (IC50 1.7 μM), and a medium amount of cytotoxicity (IC50 19.8–53.4 μM) was reported upon application of chaetomugilides B and C and chaetoviridin E against the same HepG2 (Li et al., 2013). Endophytic fungi *Aspergillus fumigatus* associated with plant *Cynodon dactylon* produces 9-Deacetoxyfumigaclavine C11, was shown to be cytotoxic to human leukaemia cells (K562) with IC50 3.1 μM akin to was shown to be cytotoxic to human leukaemia cells (K562) with IC50 3.1 μM akin to doxorubicin hydrochloride (1.2 μM), a drug currently used in leukaemia (Liu et al., 2004). *Eurotium rubrum* a fungal endophyte, isolated from tissues of the plant *Hibiscus tiliaceus* showed the presence of variecolorin grand alkaloid E-7 that are alkaloid compound along with the presence of a dioxopiperazine alkaloid (Wang et al., 2007). From the leaf tissues of *Desmotes incomparabilis* isolated an endophytic fungus under *Mycoleptodiscus* sp. produces Mycoleptodiscus B, which exhibits anticancer activity against lung, skin and prostate carcinoma cell lines (H460, A2508, H522-T1, PC-3 and IMR-90) displaying IC50 values of 0.660, 0.780, 0.630, 0.600, 0.41 μM (Ortega et al., 2013).

Lactones

Lactones are produced by the lactonization (cyclization) of the hydroxyl acids, β oxidation; and ω oxidation are some of the pathways through which lactones are made. They are cyclic esters of polyketide origin (Krzyczkowska et al., 2017). A potent lactone called radicicol was isolated from *Chaetomium chiversii* from Ephedra fasciculate and represented a promising agent inhibiting the proliferation of the MCF-7 cell line (Turbyville et al., 2006). Myrotheciumone is a bicyclic lactone produced by *Myrothecium roridum* inhabiting *Ajuga decumbens*, a medicinal herb that exhibits cytotoxicity against HepG2, SMMc-7721, A549, MCF-7, QSG-7701 and HL-7702 cell lines (Lin et al., 2014). Photipyrone B is a compound obtained from

the endophytic fungi *Pestalotiopsis photiniae* isolated from the plant *Roystonea Regia*. China. It shows an inhibitory effect against MDA-MB-231(Ding et al., 2012). Another compound called Brefeldin A exhibits antiviral, anticancer and antifungal activities and it was isolated from multiple fungi, for example, Alternaria, Ascochyta, *Aspergillus clavatus*, *Paecilomyces* sp., Curvularia, and Cercospora. Penicillium and Phyllosticta (Wang et al., 2002).

Terpenoids

Terpenoids are modified terpenes, and terpenes are biosynthetically derived from the isoprene unit. Isoprene units are the basic units of terpenes. Isoprene units are simple skeleton-like structures containing five carbon atoms, they are diverse naturally occurring compounds with immense therapeutic potential. Biosynthesized through the mevalonate pathway using enzyme terpene cyclase enzymes. Approximately 50,000 terpenoid metabolites are there which include monoterpenes, sesquiterpenes, and di-terpenes representing nearly 400 distinct structural families, isolated from plants, fungi and bacteria. Biologically active terpenoid compounds are produced by many endophytic fungi, they are the potent producers of terpenoid compounds. (+)-(3S,6S,7R,8S)-periconone A and (−)-(1R,4R,6S,7S)- 2-caren-4,8-olide, are two new terpenoids obtained from the endophytic fungus *Periconia* sp. isolated from the plant *Annona muricata.* Against six human tumour cell lines (HCT-8, Bel-7402, BGC-823, A549, A2780 and MCF7) with IC50>10−5 M, these two compounds show low cytotoxic activity during in-vitro assays (Ge et al., 2011). All these widely occurring metabolites, relatively a minor fraction occur in prokaryotes (Yamada et al., 2015). Generation of reactive oxygen species (ROS) in *A. lancea* (a Chinese medicinal plant that contains oxygenous sesquiterpenoids) may lead to the increased oxygenous sesquiterpenoid content and the switching of this ROS can be done by the endophytic bacterium *Pseudomonas fluorescens* ALEB7B (Zhou et al., 2015).

Artemisinin isolated from the *A. annua* is a sesquiterpene lactone with potential active antimalarial principle by Tu Youyou (Woodrow et al., 2005). There is evidence for the existence of many more biological activities for artemisinin including anti-inflammatory, immunoregulatory, and anticancer activities without any risk of drug-resistant development (Das 2015). Phomoarcherins A-Ce three novel sesquiterpenes obtained from the *Phomopsis archeri* endophyte residing inside the stem of *Vanilla albidia.* Among these compounds, Phomoarcherin B exhibited in vitro cytotoxic activity against KKU-100, KKU-M139, KKU-M156, KKU-M213, KKUM214 and KB cell lines with IC50 values of 8.0, 0.1, 2.0, 20, 5.0 and 9.4 μg/mL respectively. Phomoarcherin C exhibited in vitro cytotoxic activity against KKU-100, KKU-M139, KKU-M156, KKU-M213 and KKU-M214 cell lines with IC50 values 8.9, 8.9, 18.0, 15.4, and 18.8 μg/mL respectively. Phomoarcherin A exhibited in vitro cytotoxic activity against KKU-M213 cell lines with IC50 values of 16.6 (Hemtasin et al., 2011). *Paraconiothyrium* sp. MY-42 a fungal endophyte was used to isolate isopimarane diterpenes, which shows a medium degree of cytotoxic activity against promyelocytic HL60 cells in human leukaemia (Shiono et al., 2011). Geopyxin B is a novel ent-kauranediterpenoid isolated from *Geopyxis* aff. *majalis* shows cytotoxic effect towards NCI-H460, SF-268, MCF-7, PC3M and MDA-MB-231 cell lines with IC50 values of 2.25, 2.35, 4.32, 5.41 and 3.31 μM respectively (Wijeratne et al., 2012). The main bioactive component present in fruits and bark of traditional anthelmintic and insecticidal plants *Melia azedarach* and *Melia toosendan* is called Triterpenoid toosendanin (TSN) (Wang et al., 2007). TSN acts as a potential antitumor drug against various tumours and involves inhibition of STAT3 an emerging target for cancer therapy, induction of estrogen receptor β (ERβ) and p53 proteins, and activation of the mitochondrial apoptotic pathway (Gao et al., 2019)

Sesquiterpenes, ceriponol F, ceriponol G and ceriponol K was extracted from the fungus *Ceriporia lacerate* inhabiting a medicinal plant *Huperzia serrata* (Chen et al., 2016). Cerpinol F and cerpinol K show moderate cytotoxic activity against HeLa, HepG2 and SGC 7901 (IC50 32.3 ± 0.4–173.2 ± 1.5 μM). Whereas ceriponol G shows somewhat improved cytotoxicity towards HeLa cells (Ying et al., 2013).

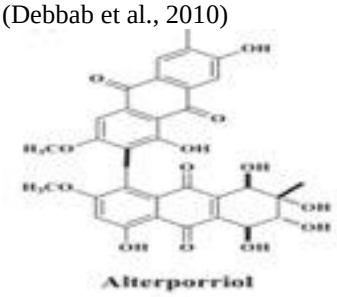
Cercosporene F is a new guanacastane diterpene obtained from an endophytic fungi *Cercospora* sp. isolated from the leaves of *Fallopia japonica*. The fungus *Cercosporene* F exhibits cytotoxic activities against five human tumour cell lines viz. HeLa, A549, MCF-7, HCT116 and T24 with IC50 values of 19.3, 29.7, 46.1, 21.3, and 8.16 μM respectively (Feng et al., 2014)

Forskolin is a biologically active labdane diterpene compound isolated from the roots of Indian Coleus (*Coleus forskohlii*) which is characterized by anti-HIV, and antitumor activities. Other approved uses of forskolin include hypertension and heart failure to lipolysis and body weight control (Pateraki et al., 2017). Compound Perenniporin A was isolated from *Perenniporia tephropora* Z41 an endophytic fungus inhabiting in bark of *Taxus chinensis* var. mairei showed only a moderate amount of cytotoxicity towards HeLa, SMMC-7721, PANC-1 cell lines with IC50 values of 30.44, 45.49, 44.22 μg/mL respectively (Wu et al., 2013).

One azaphilone and two meroterpenes were isolated from an endophytic fungus penicillium from seawater. These three compounds exhibit cytotoxicity against MDA-MB-435, HepG2, HCT116 and A549 cell lines with IC50 values 34.25, 24.56, 33.72, 37.82 μM (Li et al., 2014).

Quinones

Quinones are widely distributed among plant kingdom, mainly in higher plants those from the families such as Leguminosae, Polygonaceae, Rubiaceae, Boraginaceae, Rhamnaceae, Labiatae (Tyagi et al., 2021). Usually, they are present in various living organisms like plants, humans, and bacteria and their conjugated structure was derived from fungi. Endophytic fungi *Eurotium rubrum* isolated from the inner tissues of the mangrove plant *Hibiscus tiliaceous* produces a compound called 9-dehydroxyeurotinone which shows anticancer activity against SW1990 cell lines with IC50 of 25 µg/mL (Chen et al., 2016). Novel cytotoxic compound 2,3-didehydro-19α-hydroxy14-epicochlioquinone B isolated from *Nigrospora* sp. MA75 residing in the stem of the marine mangrove plant *Pongamia pinnata.* Displayed cytotoxicity towards MCF-7, SW1990, and SMMC7721 cell lines with IC50 values of 4, 5, and 7 µg/mL respectively (Li et al., 2011). According to some reports, biosynthesis of quinones occurs via the polyketide synthase pathway in Beauveria species. isoprenoid quinones are synthesized Through different pathways quinones can be synthesized for example isoprenoid quinones are synthesized by the shikimate pathway using chorismite-derived compounds as precursors, terrequinone by NRPS from L-tryptophan, dopaquinone by tyrosinase from tyrosine, and benzoquinone by catechol oxidase/PKS from catechol (Feng et al., 2015). Quinones are derivatives of aromatic compounds such as benzene or naphthalene. An anthanoid compound alterporriol extracted from rice culture of an endophytic Stemphylium globuliferum associated with the medicinal plant *Mentha pulegium* shows cytotoxicity towards L5178Y cancer cell line, with an EC50 value of 2.7 µg/mL (Debbab et al., 2010)



Fig; 10

Anthraquinones such as Alterporriol L and alterporriol K isolated from the fungal endophyte, *Alternaria* sp. ZJ9-6B residing in mangrove *Aegiceras corniculatum*(Chen et al. 2016). During experimental analysis Alterporriol shows the medium degree of cytotoxicity towards MDA-MB-435 and MCF-7 cells (IC50 13.1– 29.1 µM) (Huang et al., 2011a).

Table 1. Novel cytotoxic compounds reported from endophytes

Compounds	Chemical nature	Cell line	Fungus	Host	References
Myrotheciumone A	Lactones	HepG2, SMMC-7721, A549, MCF-7, QSG-7701, HL-770	*Myrothecium roridum*	*Ajuga decumbens*	Lin et al., 2014
) - (4S,8S) -foedanolide (#12) (+) - (4R,8R) - foedanolide	Lactones	HeLa, A-549, U-251, HepG2, MCF-7 HeLa, A-549, U-251, HepG2, MCF-7	*Pestalotiopsis foedan*	*Bruguiera sexangula*	Yang et al., 2013
Phomopsidone A	Lactones	MDA-MB-435	*Phomopsis sp.* A123	*Kandelia candel*	Zhang et al., 2014
Cytospolide B Cytospolide E	Lactones	A-549 A-549	*Cytospora* sp. (strain No. ZW02*)*	*Ilex canariensi*	Lu et al., 2011
Asperlactone G Asperlactone H	Lactones	A-549 A-549	*Aspergillus* sp.	*Pinellia ternate* (T)	Xin et al., 2019

Compounds	Chemical nature	Cell line	Fungus	Host	References
Brefeldin A 37	Lactone	HL-60 KB MCF-7 Spc-A-1 1.0 HeLa	*Aspergillus clavatus* & *Paecilomyces* sp	*Taxus mairei* & *Torreya grandis*	Wang et al., 2002
Brefeldin A 37	Lactone	KB, BC-1, NCI-H187	*Acremonium* sp.	*Knema laurina*	
Podophyllotoxin	Lignan	Topoisomerase I	*Trametes hirsuta*	*Podophyllum hexandrum*	Puri Let al., 2006
Podophyllotoxin	Lignan	Topoisomerase I	*Phialocephala fortinii*	*Podophyllum peltatum*	Eyberger et al., 2006
Epicocconigrone A	Polyketides	RAJI	*Epicoccum nigrum*	*Mentha suaveolens*	Amrani et al., 2013
Acremoxanthone E	Polyketides	U251, PC-3, K562, HCT-15, MCF-7, SKLU-1	*Acremonium camptosporum*	*Bursera simaruba*	Meléndez-González et al., 2015
Preussilide E	Unclassified Polyketide	L929 KB3.1 A431 A-549 SKOV-3 PC-3	*Preussia similis*	*Globularia alypum* (T)	Noumeur et al., 2017
Duclauxamide A1	Polyketides	HL-60, SMML-7721, A549, MCF-7, SW48	*Penicillium manginii*	*Panax notoginseng*	Cao et al., 2015

Compounds	Chemical nature	Cell line	Fungus	Host	References
Preussilide A	Unclassified Polyketide	L929 KB3.1 A431 A-549 SKOV-3	*Preussia similis*	*Globularia alypum* (T)	Noumeur et al., (2017)
Bikaverin	Polyketide	NCI-H460 MIA Pa Ca-2 MCF-7, SF-268	*Fusarium oxysporum*	*Cylindropuntia echinocarpus*	Zhan et al., 2007
Preussilide B	Unclassified Polyketide	L929 KB3.1 A431 A-549 SKOV-3 PC-3	*Preussia similis*	*Globularia alypum* (T)	Noumeur et al., 2017
Isocochlioquinone D	Meroterpenoids	SF-268 MCF-7 NCI–H460	*Bipolaris sorokiniana* A606	*Pogostemon cablin* (T)	Wang et al., 2016
Epoxyphomalin A		MDA468 MDA-MB-231 T24 OVCAR5 OVCAR4 OVCAR3	*Peyronellaea coffeaearabicae* FT238	*Pritchardia lowreyana*	Li et al., 2016
Isopenicin A		SW480 SW620 HCT116 CaCo2 SMMC-7721 A-549	*Penicillium* sp.sh18	*Isodon eriocalyx var. laxiflora* (T)	Tang et al., 2019
Isopenicin B		SW480 SW620 HCT116 CaCo2			

Compounds	Chemical nature	Cell line	Fungus	Host	References
Talaperoxide B Talaperoxide D	Peroxides	MCF-7, MDA-MB-435, HepG2, HeLa, PC-3 MCF-7, MDA-MB-435, HepG2, HeLa, PC-3	*Talaromyces flavus*	*Sonneratia apetala*	Li et al., 2011
Cladosporone A	Others	K562, A549, HL-60, Huh-7, MCF-7, H1975, U937, BGC823, Hela, MOLT-4	*Cladosporium* sp.	*Kandelia candel*	Ai et al., 2014
Dihydronaphthalenone 5-hydroxyl dihydro fusarubin A 5-hydroxy dihydrofusarubin B	Phenolic compounds	KB, MCF-7, NCI-H187, Vero KB, MCF-7, NCI-H187, Vero KB, MCF-7, NCI-H187, Vero	*Fusarium* sp. BCC14842	*Bamboo*	Kornsakulkarn et al., 2011

Compounds	Chemical nature	Cell line	Fungus	Host	References
Penicibrocazine A	Nitrogen containing compounds (Diketopiperazine)	Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990, SW480, U251	*penicillium brocae* MA231	*Avicennia marina*	Meng et al., 2014
Penicibrocazine B		Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990, SW480, U251			
Penicibrocazine E		Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990, SW480, U251			
Penicibrocazine F		Du145, HeLa, HepG2, MCF-7, NCIH460, SGC-7901, SW1990, SW480, U2 51			
Merulin A	Terpene	BT474, SW620	XG8D(a basidiomycete)	*Xylocarpus granatum*	Chokpaiboon et al., 2010
Merulin C		BT474, SW620			

CONCLUSION

This review discussed the importance of endophytic fungi, as the source of secondary metabolites and various bioactive molecules which can be used as a natural weapon against deadly diseases. Years back endophytes gained the attention of the scientific community for their potential application in the pharmaceutical industry. Endophytes are microorganisms that live inside of healthy plant tissue in harmony with the plant environment, they exhibit complex interaction with their host for coexistence. During this time period, endophytes may develop many significant and novel characteristics. In order to maintain stable symbiosis, a variety of enzymes are involved in the process of colonization and growth. Endophytes are more useful and selective in biological conversion due to their unique habitat and they produce biologically active novel metabolites. The cytotoxic effect of the fungal metabolites under consideration is widespread, their inhibitory concentration may vary from low to high micromolar according to the tumour cell lines and the cytotoxicity may vary depending on cell lines.

In future genetic engineering, improved cultivation and fermentation techniques allow the researchers to isolate and discover new methods and fungal strains producing antitumor compounds. Evaluating the novel metabolic pathways for the mass production of metabolites paves the way for effective cancer treatment in a cost-effective manner and with fewer side effects. Therefore, exploring exploiting metabolites from endophytes will be an excellent avenue in the healthcare industry.

REFERENCE

1. Abad A, López-Pérez JL, del Olmo E, García-Fernández LF, Francesch A, Trigili C, Barasoain I, Andreu JM, Díaz JF, San Feliciano A. (2012). Synthesis and antimitotic and tubulin interaction profiles of novel pinacol derivatives of podophyllotoxins, J Med Chem. Aug 9;55(15):6724-37. Epub 2012 Jul 23. PMID: 22607205.
2. Abdelhamed S, Yokoyama S, Refaat A, Ogura K, Yagita H, Awale S, Saiki I. (2014). Piperine enhances the efficacy of TRAIL-based therapy for triple-negative breast cancer cells, Anticancer Res. Apr;34(4):1893-9. PMID: 24692724.
3. Abdel-Razek, A.S, El-Naggar, M.E, Allam A, Morsy, O.M, Othman S.I. (2020). Microbial natural products in drug discovery Processes, 8, 1–19.
4. Abdelwahab, Miada F, Tibor Kurtán, Attila Mándi, Werner E.G. Müller, Mostafa A. Fouad, Mohamed S. Kamel, Zhen Liu, Weaam Ebrahim, Georgios Daletos, Peter Proksch. (2018) Induced secondary metabolites from the endophytic fungus *Aspergillus versicolor* through bacterial co-culture and OSMAC approaches, Volume 59, Issue 27, Pages 2647-2652, ISSN 0040-4039,
5. Ai W, Lin X, Wang Z, Lu X, Mangaladoss F, Yang X, Zhou X, Tu Z, Liu Y. (2015). Cladosporone A, a new dimeric tetralone from fungus Cladosporium sp. KcFL6' derived of mangrove plant *Kandelia candel*, J Antibiot (Tokyo). Mar;68(3):213-5. doi: 10.1038/ja.2014.126. Epub 2014 Sep 24. PMID: 25248726.
6. Amna T, Puri SC, Verma V, Sharma JP, Khajuria RK, Musarrat J, Spiteller M, Qazi GN. (2006). Bioreactor studies on the endophytic fungus *Entrophospora infrequens* for the production of an anticancer alkaloid camptothecin, Can J MicrobiolMar;52(3):189-96. doi: 10.1139/w05-122. PMID: 16604115.
7. Ardalani H, Avan A, Ghayour-Mobarhan M. (2017). Podophyllotoxin: a novel potential natural anticancer agent. Avicenna J Phytomed, Jul-Aug;7(4):285-294. PMID: 28884079; PMCID: PMC5580867.
8. Arora J.and Ramawat K. G. (2017). "An introduction to endophytes," Sustainable Development and Biodiversity, Springer, vol. 15, pp. 1–23, Cham, Switzerland. CHAP, SN - 978-3-319-66540-5,
9. Aswini A, and Soundhari C. (2018). Production of camptothecin from endophytic fungi and characterization by high-performance liquid chromatography and anticancer activity against colon cancer cell line. *Asian Journal of Pharmaceutical and Clinical Research*, vol. 11, no. 3, Mar., pp. 166-70.
10. Ayob FW, Simarani K, Zainal Abidin N, Mohamad J. (2017). First report on a novel *Nigrospora sphaerica* isolated from *Catharanthus roseus* plant with anticarcinogenic properties, Microb Biotechnol. Jul;10(4):926-932. doi: 10.1111/1751-7915.12603. Epub 2017 Jun 14. PMID: 28612376; PMCID: PMC5481544.
11. Bacon C.W, White J.F. (2016). Functions, mechanisms and regulation of endophytic and epiphytic microbial communities of plants. Symbiosis 68, 87–98.
12. Balunas MJ, Kinghorn AD. (2005). Drug discovery from medicinal plants. Life Sci. 2005 Dec 22;78(5):431-41. doi: 10.1016/j.lfs.2005.09.012. Epub. PMID: 16198377.
13. Banyal A, Thakur V, Thakur R. Kumar P. (2021). Endophytic Microbial Diversity: A New Hope for the Production of Novel Anti-tumor and Anti-HIV Agents as Future Therapeutics. Curr Microbiol 78, 1699–1717 https://doi.org/10.1007/s00284-021-02359-2

14. Barnett CJ, Cullinan GJ, Gerzon K, Hoying RC, Jones WE, Newlon WM, Poore GA, Robison RL, Sweeney MJ, Todd GC, Dyke RW, Nelson RL. (1978). Structure-activity relationships of dimeric Catharanthus alkaloids. 1. Deacetylvinblastine amide (vindesine) sulfate, J Med Chem. Jan;21(1):88-96.
15. Bedi A, Adholeya A, Deshmukh SK. (2017). Novel anticancer compounds from endophytic fungi, Volume 6, No. 1 Current Biotechnology. 7:168–18.
16. Bedi, Pooja & Gupta, Richa & Pramanik, Tanay. (2018). Synthesis and biological properties of pharmaceutically important xanthones and benzoxanthone analogs: A brief review. Asian Journal of Pharmaceutical and Clinical Research. 11. 12. 10.22159/ajpcr.2018.v11i2.22426.
17. Bertrand S, Bohni N, Schnee S, Schumpp O, Gindro K, Wolfender JL. (2014). Metabolite induction via microorganism co-culture: a potential way to enhance chemical diversity for drug discovery. Biotechnol Adv. 2014 Nov 1;32(6):1180-204. 2014.03.001. Epub Mar 17. PMID: 24651031.
18. Bhalkar BN, Patil SM, Govindwar SP. (2016). Camptothecine production by mixed fermentation of two endophytic fungi from *Nothapodytes nimmoniana*. Fungal Biol. Jun-Jul;120(6-7):873-83. doi: 10.1016/j.funbio.2016.04.003. Epub 2016 Apr 12. PMID: 27268247.
19. Biswas D, Nazir R, Biswas P, Vijay K, Samapika N, Anuradha N, Dey A, Pandey, Devendra K M. (2020). Endophytic sources of diosgenin, a natural steroid with multiple therapeutic values. South African Journal of Botany. 134
20. Bjornsti M. A., Benedetti P, Viglianti G. A. and J. C. Wang. (1989). Cancer Res, 49, 6318.
21. Blagosklonny MV. (2004). Analysis of FDA approved anticancer drugs reveals the future of cancer therapy. Cell Cycle. Aug;3(8):1035-42. Epub 2004 Aug 16. PMID: 15254418.
22. Bo G, Haiyan L, Lingqi Z. (1998). Isolation of a fungus producting vinbrastine. J Yunnan Univ 20(3):214–215
23. Brito DA, Yang Z, Rieder CL. (2008). Microtubules do not promote mitotic slippage when the spindle assembly checkpoint cannot be satisfied. J Cell Biol. Aug 25;182(4):623-9. Epub 2008 Aug 18. PMID: 18710927; PMCID: PMC2518701.
24. Cao P, Yang J, Miao CP, Yan Y, Ma YT, Li XN, Zhao LX, Huang SX. (2015). New duclauxamide from Penicillium manginii YIM PH30375 and structure revision of the duclauxin family. Org Lett. Mar 6;17(5):1146-9. Epub 2015 Feb 19. PMID: 25695664.
25. Chakravarty, K., Gaur, S. (2018). Fungal Endophytes as Novel Sources of Anticancer Compounds. In: Akhtar, M., Swamy, M. (eds) Anticancer Plants: Natural Products and Biotechnological Implements. Springer, Singapore.
26. Chandra S. (20120). Endophytic fungi: novel sources of anticancer lead molecules. Appl Microbiol Biotechnol. Jul;95(1):47-59. doi: 10.1007/s00253-012-4128-7. Epub 2012 May 24. PMID: 22622838.Chandra, S. (2012). Endophytic fungi: novel sources of anticancer lead molecules. Appl. Microbiol. Biotechnol. 95, 47–59.
27. Chen J, Qiu X, Wang R, Duan L, Chen S, Luo J, Kong L. (2009b). Inhibition of human gastric carcinoma cell growth in vitro and in vivo by cladosporol isolated from the paclitaxel-producing strain *Alternaria alternata* var. monosporus. Biol Pharm Bull. 2009 Dec;32(12):2072-4. PMID: 19952432.
28. Chen JY, Tang YA, Li WS, Chiou YC, Shieh JM, Wang YC. (2013). A synthetic podophyllotoxin derivative exerts anti-cancer effects by inducing mitotic arrest and pro-apoptotic ER stress in lung cancer preclinical models. PLoS One. Apr 30;8(4):e62082.. PMID: 23646116; PMCID: PMC3639983. Chen JY, Tang YA, Li WS, Chiou YC, Shieh JM, Wang YC. A synthetic podophyllotoxin derivative exerts anti-cancer effects by inducing mitotic arrest and pro-apoptotic ER stress in lung cancer preclinical models. Plos One. 2013;8(4):e62082.
29. Chen L, Zhang QY, Jia M, Ming QL, Yue W, Rahman K, Qin LP, Han T. (2016). Endophytic fungi with antitumor activities: Their occurrence and anticancer compounds. Crit Rev Microbiol. May;42(3):454-73. Epub 2014 Oct 24. PMID: 25343583.
30. Chen Y, Liu Z, Huang Y, Liu L, He J, Wang L, Yuan J, She Z. (2019). Ascomylactams A–C, cytotoxic 12- or 13-membered-ring macrocyclic alkaloids isolated from the mangrove endophytic fungus Didymella sp. CYSK-4, and structure revisions of Phomapyrrolidones A and C. J Nat Prod 82(7):1752–1758.
31. Chithra S, Jasim B, Anisha C, Mathew J, Radhakrishnan EK. (2014). LC-MS/MS based identification of piperine production by endophytic Mycosphaerella sp. PF13 from *Piper nigrum.* Appl Biochem Biotechnol. May;173(1):30-5. doi: 10.1007/s12010-014-0832-3. Epub 2014 Apr 2. PMID: 24691878.
32. Chithra S, Jasim B, Sachidanandan P, Jyothis M, Radhakrishnan EK. (2017). Piperine production by endophytic fungus *Colletotrichum gloeosporioides* isolated from *Piper nigrum*. Phytomedicine. Mar 15;21(4):534-40. doi: 10.1016/j.phymed.2013.10.020. Epub 2013 Nov 21. PMID: 24268806.
33. Chokpaiboon S, Sommit D, Teerawatananond T, Muangsin N, Bunyapaiboonsri T and Pudhom K J. (2010). Cytotoxic Nor-chamigrane and Chamigrane Endoperoxides from a Basidiomycetous Fungus. Journal of natural products. 73. 1005-7. 10.1021/np100103j. Nat. Prod., 2010, 73, 1005–1007
34. Clarance, P., Khusro, A., Lalitha, J., Sales, J., & Paul, A. (2019). Optimization of camptothecin production and biomass yield from endophytic fungus *Fusarium solani* strain ATLOY-8. *Journal of Applied Pharmaceutical Science*.
35. Cortés F, Pastor N. (2003). Induction of endoreduplication by topoisomerase II catalytic inhibitors. Mutagenesis. Mar;18(2):105-12. doi: 10.1093/mutage/18.2.105. PMID: 12621064.
36. Cragg GM, Boyd MR, Cardellina II JH, Grever MR, Schepartz S, Snader KM, Suffness M. (1993): The search for new pharmaceutical crops: Drug discovery and development at the National Cancer Institute. In: Janick J, Simon JE, eds., New Crops. New York, Wiley, pp. 161–167.
37. Dancey J, Eisenhauer EA. (1996). Current perspectives on camptothecins in cancer treatment. Br J Cancer. Aug;74(3):327-38. doi: 10.1038/bjc.1996.362. PMID: 8695345; PMCID: PMC2074644.
38. Das AK. (2015). Anticancer Effect of AntiMalarial Artemisinin Compounds. Ann Med Health Sci Res. Mar-Apr;5(2):93-102. doi: 10.4103/2141-9248.153609. PMID: 25861527; PMCID: PMC4389338.
39. de Andrade JP, Guo Y, Font-Bardia M, Calvet T, Dutilh J, Viladomat F, Codina C, Nair JJ, Zuanazzi JAS, Bastida J. (2014). Crinine-type alkaloids from *Hippeastrum aulicum* and *H. calyptratum*. Phytochemistry. 2014 Jul;103:188-195. j.phytochem.2014.03.007. Epub. PMID: 24768284.
40. Debbab A, Amal H. Aly, Wen H. Lin, Proksch P. (2010). Bioactive Compounds from Marine Bacteria and Fungi, Volume3, Issue5, Special Issue: Marine Omics.
41. Demain AL, Vaishnav P. (2011). Natural products for cancer chemotherapy. Microb Biotechnol. Nov;4(6):687-99. doi: 10.1111/j.1751-7915.2010.00221.x. Epub 2010 Nov 18. PMID: 21375717; PMCID: PMC3815406
42. Dhayanithy G, Subban K, Chelliah J. (2019). Diversity and biological activities of endophytic fungi associated with *Catharanthus roseus*. BMC Microbiol. Jan 21;19(1):22. PMID: 30665368; PMCID: PMC6341747.
43. Ding G, Qi Y, Liu S, Guo L, Chen X. (2012). Photipyrones A and B, new pyrone derivatives from the plant endophytic fungus Pestalotiopsis photiniae. J Antibiot (Tokyo). May;65(5):271-3. doi: 10.1038/ja.2012.14. Epub 2012 Mar 14. PMID: 22415458.
44. Doucette CD, Hilchie AL, Liwski R, Hoskin DW. (2013). Piperine, a dietary phytochemical, inhibits angiogenesis. J Nutr Biochem. Jan;24(1):231-9. Epub 2012 Aug 16. PMID: 22902327; PMCID: PMC3524266.

45. Drukman S, Kavallaris M. (2002). Microtubule alterations and resistance to tubulin-binding agents (review). Int J Oncol. Sep;21(3):621-8. PMID: 12168109.
46. Dudeja, S. S., & Giri, R. (2014). Beneficial properties, colonization, establishment and molecular diversity of endophytic bacteria in legumes and non-legumes. African Journal of Microbiology Research, 8(15), 1562-1572
47. Ehab S. Elkhayat, Asmaa Mohamed Goda. (2017). Antifungal and cytotoxic constituents from the endophytic fungus Penicillium sp., Bulletin of Faculty of Pharmacy, Cairo University, Volume 55, Issue 1, Pages 85-89, ISSN 1110-0931,
48. El Amrani M, Lai D, Debbab A, Aly AH, Siems K, Seidel C, Schnekenburger M, Gaigneaux A, Diederich M, Feger D, Lin W, Proksch P. (2013). Protein kinase and HDAC inhibitors from the endophytic fungus *Epicoccum nigrum*. J Nat Prod. 2014 Jan 24;77(1):49-56. doi: 10.1021/np4005745. PMID: 24328302.
49. El-Tarabily K, Hardy SJ, Krishnapillai S. (2010. Performance of three endophytic actinomycetes in relation to plant growth promotion and biological control of *Pythium aphanidermatum*, a pathogen of cucumber under commercial field production conditions in the United Arab Emirates. Eur J Plant Pathol 128(4):527–539
50. Evidente A. and Kornienko, A. (2009). Anticancer evaluation of structurally diverse Amaryllidaceae alkaloids and their synthetic derivatives. Phytochemistry Reviews, vol. 8, no. 2, pp. 449–459,
51. Eyberger AL, Dondapati R, Porter JR. (2006). Endophyte fungal isolates from *Podophyllum peltatum* produce podophyllotoxin. J Nat Prod. 69(8):1121-4. PMID: 16933860.
52. Farias KJS, Machado PRL, de Almeida Júnior RF, Lopes da Fonseca BA. (2019). Brefeldin A and Cytochalasin B reduce dengue virus replication in cell cultures but do not protect mice against viral challenge. Access Microbiol.;1(6):e000041. doi: 10.1099/acmi.0.000041. PMID: 32974532; PMCID: PMC7470301.
53. Feher M, Schmidt JM .(2003) .Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry. J Chem Inf Comput Sci 43(1):218–227.
54. Feng P, Shang Y, Cen K, Wang C. (2015). Fungal biosynthesis of the *Bibenzoquinone oosporein* to evade insect immunity. Proc Natl Acad Sci U S A. 112(36):11365-70. doi: 10.1073/pnas.1503200112. Epub 2015 Aug 24. PMID: 26305932; PMCID: PMC4568701.
55. Feng Y, Ren F, Niu S, Wang L, Li L, Liu X, Che Y. (2014). Guanacastane diterpenoids from the plant endophytic fungus Cercospora sp. J Nat Prod. Apr 25;77(4):873-81. doi: 10.1021/np4009688. Epub 2014 Feb 27. PMID: 24576210.
56. Ferlini C, Raspaglio G, Mozzetti S, Distefano M, Filippetti F, Martinelli E, Ferrandina G, Gallo D, Ranelletti FO, Scambia G. (2003). 4Bcl-2 down-regulation is a novel mechanism of paclitaxel resistance. Mol Pharmacol. (1):51-8. PMID: 12815160.
57. Fiołka M J, Grzywnowicz K, Rzymowska J, Lewtak K, Szewczyk R, Mendyk E, Keller R. (2015). Antitumour and apoptotic effects of a novel Tris-peptide complex obtained after isolation of *Raoultella ornithinolytica* extracellular metabolites. J Appl Microbiol. 2015 Jun;118(6):1357-69. doi: 10.1111/jam.12806. Epub. PMID: 25809524.
58. Fiołka M J, Lewtak K, Rzymowska J, Grzywnowicz K, Monika Hułas-Stasiak, Sofińska-Chmiel W, Skrzypiec. (2013). Antifungal and anticancer effects of a polysaccharide–protein complex from the gut bacterium *Raoultella ornithinolytica* isolated from the earthworm Dendrobaena veneta, Pathogens and Disease, Volume 69, Issue 1, Pages 49–61,
59. Flores-Bustamante, Z. R., Rivera-Ordũa, F. N., Martínez-Cárdenas, A., & Flores-Cotera, L. B. (2010). Microbial paclitaxel: Advances and perspectives. Journal of Antibiotics, 63(8), 460-467.
60. Gao T, Xie A, Liu X, Zhan H, Zeng J, Dai M, Zhang B. (2019). Toosendanin induces the apoptosis of human Ewing's sarcoma cells via the mitochondrial apoptotic pathway. Mol Med Rep. 2019 Jul;20(1):135-140. doi: 10.3892/mmr.10224. Epub May 9. PMID: 31115517; PMCID: PMC6579966.
61. Gao Y, Lu Q, Pu Zang P, Li Xue, Ji Qing, He Zhongmei, Yan Zhao, He Yang, Xueliang Zhao, Lianxue Zhang. (2015). An endophytic bacterium isolated from Panax ginseng C.A. Meyer enhances growth, reduces morbidity, and stimulates ginsenoside biosynthesis, Phytochemistry Letters, Volume 11, 2015, Pages 132-138, ISSN 1874-3900, j.phytol.2014.12.007
62. Ge HL, Zhang DW, Li L, Xie D, Zou JH, Si YK, Dai J. (2011). Two new terpenoids from endophytic fungus Periconia sp. F-31. Chem Pharm Bull (Tokyo).;59(12):1541-4. PMID: 22130377.
63. Gordaliza M. (2007). Natural products as leads to anticancer drugs. Clin Transl Oncol 9(12):767–776. https://doi.org/10.1007/s12094-007-0138-9
64. Gouda S, Das G, Sen SK, Shin HS, Patra JK. (2016). Endophytes: A Treasure House of Bioactive Compounds of Medicinal Importance. Front Microbiol. 29;7:1538. doi: 10.3389/fmicb.2016.01538. PMID: 27746767; PMCID: PMC5041141.
65. Granados GM, McTaggart AR, Rodas CA, Roux J, Wingfield MJ. (2020). Species of *Cryphonectriaceae* occupy an endophytic niche in the Melastomataceae and are putative latent pathogens of Eucalyptus. European Journal of Plant Pathology 156(1):273–283.
66. Grover P, Bhardwaj M, Mehta L, Kapoor G, Chawla PA. (2022). Current Developments in the Pyran-Based Analogues as Anticancer Agents. Anticancer Agents Med Chem. 2022;22(19):3239-3268. PMID: 34802409.
67. Guerram M, Jiang ZZ, Zhang LY. (2012). Podophyllotoxin, a medicinal agent of plant origin: past, present and future. Chinese Journal of Natural Medicines, Volume 10, Issue 3, Pages 161-169, ISSN 1875-5364
68. Gulyamova T Abdulmyanova L, Ruzieva D, Rasulova G, Yusupov U, Sattarova R. (2019). Effect of epigenetic modifiers on fermentation parameters of endophytic fungi from plants growing in Uzbekistan. International Journal of Current Microbiology and Applied Sciences, 8, 2019 344–1351.
69. Guo B, Li H, Zhang L. (1998). Isolation of the fungus producing vinblastine. J Yunnan University Nat Sci Edition. 1998;20:2145
70. Hawksworth DL, Lücking R. (2017). Fungal Diversity Revisited: 2.2 to 3.8 Million Species. Microbiol Spectr.;5(4). FUNK-0052-2016. PMID: 28752818.
71. Hemtasin C, Kanokmedhakul S, Kanokmedhakul K, Hahnvajanawong C, Soytong K, Prabpai S, Kongsaeree P. (2011). Cytotoxic pentacyclic and tetracyclic aromatic sesquiterpenes from Phomopsis archeri. J Nat Prod. 2011 Apr 25;74(4):609-13. Epub. PMID: 21341709.
72. Hsieh P W, Li-Chi H, Lai C H, Chin-Chung W, Tsong-Long H, Yin-Ku L, Yang-Chang W. (2009). Evaluation of the bioactivities of extracts of endophytes isolated from Taiwanese herbal plants VL - 25, DOI-10.1007/s11274-009-0036-0, World Journal of Microbiology and Biotechnology,1461-1469
73. Huang CH, Pan JH, Chen B, Yu M, Huang HB, Zhu X, YJ L, She ZG, Lin YC. (2011). Three bianthraquinone derivatives from the mangrove endophytic fungus Alternaria sp. ZJ9-6B from the South China Sea. Mar Drugs 9:832–843
74. Hwang YP, Yun HJ, Kim HG, Han EH, Choi JH, Chung YC, Jeong HG. (2011). Suppression of phorbol-12-myristate-13-acetate-induced tumor cell invasion by piperine via the inhibition of PKCα/ERK1/2-dependent matrix metalloproteinase-9 expression. Toxicol Lett. 203(1):9-19. Epub 2011 Feb 24. PMID: 21354279.
75. Jalgaonwala, R. E., Mohite, B. V., and Mahajan, R. T. (2017). A review: natural products from plant associated endophytic fungi. J. Microbiol. Biotechnol. Res. 1, 21–32.

76. Ji Y, Bi JN, Yan B, Zhu XD. (2006). Taxol-producing fungi: a new approach to industrial production of taxol. Chin J Biotechnol 22:1–6
77. Johnson, I. S, Armstrong J. G, Gorman M, Burnett J. P. Jr. (1963). The vinca alkaloids: a new class of oncolytic agents. Cancer Res. 23, 1390–1427.
78. Joshi RD, Kulkarni NS. (2016). Optimization studies on L-asparaginase production from endophytic bacteria. Int J Appl Res 2:624–629
79. Kai G, Wu C, Gen L, Zhang L, Cui L, Ni X. (2015). Biosynthesis and biotechnological production of anti-cancer drug Camptothecin. Phytochem. Rev. 14, 525–539.
80. Kala, C.P., Dhyani, P.P. & Sajwan, B.S. (2006). Developing the medicinal plants sector in northern India: challenges and opportunities. J Ethnobiology Ethnomedicine 2.
81. Kämpfer P. (2006). The family Streptomycetaceae, part I: taxonomy. In: Dworkin M (ed) The prokaryotes, vol. 3 Springer, Berlin, pp 538–604
82. Kang S H, Cao J.C, Mo L J.J, Hyde K.D. (2014). Medicinal plant endophytes produce analogous bioactive compounds. Chiang Mai Journal of Science 41, 1–13.
83. Karar J, Maity A. (2011). PI3K/AKT/mTOR pathway in angiogenesis. Front Mol Neurosci 4:51. https://doi.org/10.3389/fnmol .2011.00051.
84. Kaur P, Pandey D.K, Gupta R.C, Dey A. (2019). Simultaneous microwave assisted extraction and HPTLC quantification of mangiferin, amarogentin, and swertiamarin in Swertia species from Western Himalayas. Industrial Crops and Products 132, 449–459
85. Kaur R, Kaur G, Gill R. K, Soni R, Bariwal J. (2014). Recent developments in tubulin polymerization inhibitors: an overview. Eur. J. Med. Chem. 87, 89–124.
86. Keshri P K, Rai N, Verma, A, Swapnil C. Kamble, Barik S, Mishra P, Kumar S S, Salvi P, Gautamet V. (2021). Biological potential of bioactive metabolites derived from fungal endophytes associated with medicinal plants. Mycol Progress 20, 577–594
87. Khalifa M, Attia E, Fahim J, and M. Kamel. (2018). "An overview on the chemical and biological aspects of lycorine alkaloid," Journal of Advanced Biomedical and Pharmaceutical Sciences, vol. 1, no. 2, pp. 41–49, 201
88. Khan A.L, Gilani S.A, Waqas M, Al-Hosni K, Al-Khiziri S, Kim Y.H, Ali L, Kang S.M, Asaf S, Shahzad R, Hussain J. (2017). Endophytes from medicinal plants and their potential for producing indole acetic acid, improving seed germination and mitigating oxidative stress. Jounal of Zhejiang University-Science B 18, 125–137
89. Kharwar RN, Mishra A, Gond SK, Stierle A, Stierle D. (2011). Anticancer compounds derived from fungal endophytes: their importance and future challenges. Nat Prod Rep 28:1208–1228
90. Kim YS, Farrar W, Colburn NH, Milner JA. (2012). Cancer stem cells: potential target for bioactive food components. J Nutr Biochem 23(7):691–698.
91. Kornsakulkarn J, Dolsophon K, Boonyuen N, Boonruangprapa T, Rachtawee P, Prabpai S. (2011). Dihydronaphthalenones from endophytic fungus Fusarium sp. BCC14842. Tetrahedron; 67(39): 7540- 7.
92. Kour A, Shawl A. S, Rehman S, Sultan P, Qazi P. H, Suden P, Ravi K, Verma V. (2008). Isolation and identifcation of an endophytic strain of Fusarium oxysporum producing podophyllotoxin from *Juniperus recurva*. World Journal of Microbiology and Biotechnology, 24, 1115–1121 VL - 24.
93. Krown S. E, Moser C. B, MacPhail P, Matining R. M, Godfrey C, Caruso S. R, Gottshall B. (2020). Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: A three-arm, open-label, randomised, non-inferiority trial. The Lancet, 395, 1195–1207
94. Krzyczkowska J, Phan-Thi H, Waché Y. (2017). Lactone formation in yeast and fungi. In: Mérillon J-M, Ramawat KG (eds) Fungal metabolites. Springer International Publishing, Cham, pp 461
95. Kumar A, O'Bryan J, Krause PJ. (2021). Correction: Kumar et al. The Global Emergence of Human Babesiosis. Pathogens 2021, 10, 1447. Pathogens. 2022 Aug 17;11(8):923. doi: 10.3390/pathogens11080923. Erratum for: Pathogens. 2021 Nov 06;10(11): PMID: 36015072; PMCID: PMC9415982.
96. Kumar A, Patil D, Rajamohanan PR, Ahmad A. (2013). Isolation, purifcation and characterization of vinblastine and vincristine from endophytic fungus *Fusarium oxysporum* isolated from *Catharanthus roseus*. PLoS ONE 8(9):e71805.
97. Kumar A. (2016). 3. IJMPS - vincristine and vinblastine a review, International Journal of Medicine and Pharmaceutical Science (IJMPS) ISSN(P): 2250-0049; ISSN(E): 2321-0095 Vol. 6, Issue 1,
98. Kumar G, Chandra P, Choudhary M. (2017). Chemical science review and letters endophytic fungi: a potential source of bioactive compounds. Chem Sci Rev Lett 6(24):2373–2381
99. Kumar P, Barua C C, Sulakhiya K, Sharma R. (2017). Curcumin ameliorates cisplatin-induced nephrotoxicity and potentiates its anticancer activity in SD rats: Potential role of curcumin in breast cancer chemotherapy.Front Pharmacol. 8, 132. [CrossRef]
100. Kusari S, Lamshoft M, Spiteller M. (2009), Aspergillus *Fumigatus Fresenius*, an endophytic fungus from Juniperus communis L. Horstmann as a novel source of the anticancer pro-drug deoxypodophyllotoxin. J Appl Microbiol.;107:1019–30.
101. Kusari S, Zühlke S, Spiteller M. (2009). An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues. J Nat Prod. 2009 Jan;72(1):2-7. doi: 10.1021/np800455b. PMID: 19119919.
102. Lau DH, Xue L, Young LJ, Burke PA, Cheung AT. (1999). Paclitaxel (Taxol): an inhibitor of angiogenesis in a highly vas-cularized transgenic breast cancer. Cancer Biother Radiopharm.;14(1):31–3610
103. Li C.S, Ren G, Yang B.J, Miklossy G, Turkson J, Fei P, Ding Y, Walker L.A, Cao S. (2016). Meroterpenoids with antiproliferative activity from a Hawaiian-plant associated fungus *Peyronellaea coffeae-arabicae* FT238. Org. Lett. 18, 2335–2338.
104. Li H, Huang H, Shao C, Huang H, Jiang J, Zhu X, Liu Y, Liu L, Lu Y, Li M, Lin Y, She Z. (2011). Cytotoxic norsesquiterpene peroxides from the endophytic fungus Talaromyces flavus isolated from the mangrove plant Sonneratia apetala. J Nat Prod. 2011 May 27;74(5):1230-5. doi: 10.1021/np200164k. Epub. PMID: 21545109.
105. Li J, Sun H, Jin L, Cao W, Zhang J, Guo CY, Ding K, Luo C, Ye WC, Jiang RW. (2013). Alleviation of podophyllotoxin toxicity using coexisting flavonoids from *Dysosma versipellis*. PLoS One;8(8):e72099. doi: 10.1371/journal.pone.0072099. PMID: 23991049; PMCID: PMC3749096.
106. Li J, Yang X, Lin Y, Yuan J, Lu Y, Zhu X. (2014). Meroterpenes and azaphilones from marine mangrove endophytic fungus Penicillium 303#. Fitoterapia; 97: 241-6
107. Li J. Y, Sidhu R. S, Ford E, Long D, Hess W, Strobel G. (1998). The induction of taxol production in the endophytic fungus—Periconia sp. from *Torreya grandifolia*. Journal of Industrial Microbiology Biotechnology, 20, 259–264
108. Li S, Lei Y, Jia Y, Li N, Wink M, Ma Y. (2011). Piperine, a piperidine alkaloid from *Piper nigrum* re-sensitizes P-gp, MRP1 and BCRP dependent multidrug resistant cancer cells. Phytomedicine 19(1):83–87. https://doi.org/10.1016/j.phymed.2011.06.031
109. Liang, Z., Zhang, J., Zhang, X., Li, J., Zhang, X., and Zhao, C. (2016). Endophytic fungus from *Sinopodophyllum emodi* (Wall.) yinghat produces podophyllotoxin. J. Chromatogr. Sci. 54, 175–178. doi: 10.1093/chromsci/bmv124

110. Lin T, Wang G, Shan W, Zeng D, Ding R, Jiang X, Zhu D, Liu X, Yang S, Chen H. (2014). Myrotheciumones: bicyclic cytotoxic lactones isolated from an endophytic fungus of Ajuga decumbens. Bioorg Med Chem Lett. 2014 Jun 1;24(11):2504-7. doi: 10.1016/j.bmcl.2014.04.016. Epub. PMID: 24775302.
111. Lin T, Wang G, Shan W, Zeng D, Ding R, Jiang X, Zhu D, Liu X, Yang S, Chen H. (2014). Myrotheciumones: bicyclic cytotoxic lactones isolated from an endophytic fungus of *Ajuga decumbens*. Bioorg Med Chem Lett 24:2504–2507. https://doi.org/10.1016/j.bmcl. 2014.04.016
112. Lissoni P, Fugamalli E, Malugani F, Ardizzoia A, Secondino S, Tancini G, Gardani GS. (2000). Chemotherapy and angiogenesis in advanced cancer: vascular endothelial growth factor (VEGF) decline as predictor of disease control during taxol therapy in metastatic breast cancer. Int J Biol Markers;15(4):308-11. doi: 10.1177/172460080001500405. PMID: 11192826.
113. Liu D, Li XM, Meng L, Li CS, Gao SS, Shang Z, Proksch P, Huang CG, Wang BG. (2011a). Nigerapyrones A–H, a-pyrone derivatives from the marine mangrove-derived endophytic fungus *Aspergillus niger* MA-132. J Nat Prod 74:1787–1791
114. Liu H. X, Tan H. B, Chen Y. C, Li S. N, Li H. H, Zhang W. M. (2020). Cytotoxic triquinanetype sesquiterpenoids from the endophytic fungus Cerrena sp. A593. Natural Product Research, 34, 2430–2436
115. Liu JY, Song YC, Zhang Z, Wang L, Guo ZJ, Zou WX, Tan RX. (2004). *Aspergillus fumigatus* CY018, an endophytic fungus in *Cynodon dactylon* as a versatile producer of new and bioactive metabolites. J Biotechnol 114:279–287. https://doi.org/10.1016/j.jbiot ec.2004.07.008
116. Liu LF, Desai SD, Li TK, Mao Y, Sun M, Sim SP. (2000). Mechanism of action of camptothecin. Ann N Y Acad Sci 922:1–10. https://doi.org/10.1111/j.1749-6632.2000.tb07020.x
117. Lu S, Kurtán T, Yang G, Sun, Mándi A, Krohn K, Draeger S, Schulz B, Yi Y, Li L, Zhang W. (2011). Cytospolides A–E, new nonanolides from an endophytic fungus, Cytospora sp. Eur J Org Chem; (28): 5452-9**,** https://doi.org/10.1002/ejoc.201100675
118. Ludwig-Müller J. (2015).Plants and endophytes: equal partners in secondary metabolite production? Biotechnol Lett. (7):1325-34. doi: 10.1007/s10529-015-1814-4. Epub 2015 Mar 20. PMID: 25792513.J.
119. Lutfa A, Munir E, Yurnaliza Y, Basyuni M. (2021). Chemical analysis and anticancer activity of sesterterpenoid from an endophytic fungus Hypomontagnella monticulosa Zg15SU and its host Zingiber grifthii Baker. Heliyon 7(2):e06292. https://doi.org/10. 1016/j.heliyon.2021.e06292
120. M. J. Fiołka, K. Grzywnowicz, J. Rzymowska et al., "Antitumour and apoptotic effects of a novel tris-peptide complex obtained after isolation of Raoultella ornithinolytica extracellular metabolites," Journal of Applied Microbiology, vol. 118, no. 6, pp. 1357–1369, 2015
121. Majumder A, Jha S. (2009). Biotechnological approaches for the production of potential anticancer leads podophyllotoxin and paclitaxel: an overview. J Bio Sci 1:46–69.
122. Manayi A, Nabavi SM, Setzer WN, Jafari S. (2019). Piperine as a potential anti-cancer agent: a review on preclinical studies. Curr Med Chem 25(37):4918–4928. https://doi.org/10.2174/09298 67324666170523120656
123. Manci N, Marchetti C, Di Tucci C, Giorgini M, Esposito F, Palaia I, Musella A, Perniola G, Carrone A, Benedetti Panici P. A. (2011). prospective phase II study of topotecan (Hycamtin®) and cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer. Gynecol Oncol. 2011 Aug;122(2):285-90. doi: 10.1016/j.ygyno.2011.04.013. Epub PMID: 21555147.
124. Manjunatha B.L, Singh H.R, Ravikanth G, Nataraja K.N, Shankar R, Kumar S, Shaanker R.U. (2016). Transcriptome analysis of stem wood of Nothapodytes nimmoniana (Graham) Mabb. identifies genes associated with biosynthesis of camptothecin, an anti-carcinogenic molecule. Journal of Biosciences 41, 119–131.
125. Meléndez-González C, Murià-González MJ, Anaya AL, Hernández-Bautista BE, Hernández-Ortega S, González MC. (2015). Acremoxanthone E, a novel member of heterodimeric polyketides with a bicyclo [3.2. 2] nonene ring, produced by Acremonium camptosporum W. Gams (Clavicipitaceae) endophytic fungus. Chem Biodiversity; 12(1): 133-47.
126. Meng L-H, Li X-M, Lv C-T, Huang C-G, Wang B-G. (2014). Brocazines A–F, cytotoxic bisthiodiketopiperazine derivatives from Penicillium brocae MA-231, an endophytic fungus derived from the marine mangrove plant Avicennia marina. J Nat Prod; 77(8): 1921-7.
127. Mérino D, Lalaoui N, Morizot A, Solary E, Micheau O. (2007). TRAIL in cancer therapy: present and future challenges. Expert Opin Therap Targets 11(10):1299–1314. https://doi. org/10.1517/14728222.11.10.1299
128. Metwaly AM, Fronczek FR, Ma G, Kadry HA, El-Hela AA, Mohammad A-EI. (2014). Antileukemic α-pyrone derivatives from the endophytic fungus Alternaria phragmospora. Tetrahedron Lett; 55(24): 3478-81.
129. Mishra A, Gond SK, Kumar A, Sharma VK, Verma SK, Kharwar RN. (2011). Sourcing the fungal endophytes: a benefcial transaction of biodiversity, bioactive natural products, plant protection and nanotechnology. Microorg Sustain Agric Biotechnol. https://doi. org/10.1007/978-94-007-2214-9_26
130. Moudi M, Go R, Yien C. Y. S, and Nazre M. (2013). Vinca alkaloids. Int. J. Prev. Med. 4, 1231–1235.
131. Musavi S.F, Dhavale A, Balakrishnan R.M. (2015). Optimization and kinetic modeling of cell-associated camptothecin production from an endophytic Fusarium oxysporum NFX06. Preparative Biochemistry and Biotechnology 45, 158–172.
132. Nadeem M, Ram M, Alam P, Ahmad MM, Mohammad A, AlQurainy F, Salim K, Abdin M. (2012). Fusarium solani, P1, a new endophytic podophyllotoxin producing fungus from roots of Podophyllum hexandrum. Afr J Microbiol Res.; 6:2493–9. https://doi.org/ 10.5897/AJMR11.1596.
133. Nadeem M, Rikhari HC, Kumar A, Palni LMS, Nandi SK. (2002). Taxol content in the bark of Himalayan Yew in relation to tree age and sex. Phytochemistry 60(6):627–631. https://doi. org/10.1016/S0031-9422(02)00115-2
134. Newman DJ, Cragg GM. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. J Nat Prod 83(3):770–803. https://doi.org/10.1021/acs.jnatp rod.9b01285.
135. Nitiss, J. L. (2009). Targeting DNA topoisomerase II in cancer chemotherapy. Nat. Rev. Cancer 9, 338–350. doi: 10.1038/nrc2607.
136. Noble R L, Beer C T Cutts J H. (1958). Role of chance observations in chemotherapy: Vinca rosea. Ann N Y Acad Sci.;76(3):882-94. doi: 10.1111/j.1749-6632. 1958.tb54906.x. PMID: 13627916..
137. Noble R. (2016). Anti-cancer alkaloids of *Vinca rosea*. Pharmacol. Orient. Plants 7, 61–78.
138. Noble R. L. (1990). The discovery of the vinca alkaloids—chemotherapeutic agents against cancer. Biochem. Cell Biol. 68, 1
139. Noumeu S.R, Helaly S.E, Jansen R, Gereke M, Stradal T.E.B, Harzallah D, Stadler M, Preussilides A.F. (2017). Bicyclic polyketides from the endophytic fungus Preussia similis with antiproliferative activity. J. Nat. Prod. 80, 1531–1540. https:// doi.org/10.1021/acs.jnatprod.7b00064
140. Ochoa-Villarreal M, Howat S, Hong S, Jang MO, Jin YW, Lee EK, Loake GJ. (2016). Plant cell culture strategies for the production of natural products. BMB Rep.;49(3):149-58. doi: 10.5483/bmbrep.2016.49.3.264. PMID: 26698871; PMCID: PMC4915229.

141. Ortega HE, Graupner PR, Asai Y, Tendyke K, Qiu D, Shen YY, Rios N, Arnold AE, Coley PD, Kursar TA, Gerwick WH, Cubilla-Rios L. (2013). Mycoleptodiscins A and B, cytotoxic alkaloids from the endophytic fungus Mycoleptodiscus sp. F0194. J Nat Prod. 2013 Apr 26;76(4):741-4. doi: 10.1021/np300792t. Epub. PMID: 23560689.
142. Ouyang DY, Zeng LH, Pan H, Xu LH, Wang Y, Liu KP, He XH. (2013). Piperine inhibits the proliferation of human prostate cancer cells via induction of cell cycle arrest and autophagy. Food Chem Toxicol. Oct; 60:424-30. doi: 10.1016/j.fct.2013.08.007. Epub 2013 Aug 9. PMID: 23939040.
143. Palem PP, Kuriakose GC, Jayabaskaran C. (2016). An endophytic fungus, Talaromyces radicus, isolated from *Catharanthus roseus*, produces vincristine and vinblastine, which induce apoptotic cell death. PLoS ONE.;11(4):e0153111. https://doi.org/10.1371/ journal. pone.0144476.
144. Parthasarathy R, Shanmuganathan R, Pugazhendhi A. (2020). Vinblastine production by the endophytic fungus Curvularia verruculosa from the leaves of *Catharanthus roseus* and its in vitro cytotoxicity against HeLa cell line. Anal Biochem. https://doi. org/10.1016/j.ab.2019.113530
145. Passarella D, Peretto B, Blasco y Yepes R, Cappelletti G, Cartelli D, Ronchi C, Snaith J, Fontana G, Danieli B, Borlak J. (2010). Synthesis and biological evaluation of novel thiocolchicine-podophyllotoxin conjugates. Eur J Med Chem. (1):219-26. doi: 10.1016/j.ejmech.2009.09.047. Epub 2009 Oct 6. PMID: 19880222.
146. Patel B, Das S, Prakash R, Yasir M. (2010). Natural bioactive compound with anticancer potential. Int J Adv Pharm Sci 1:32–41
147. Pateraki I, Andersen-Ranberg J, Jensen NB, Wubshet SG, Heskes AM, Forman V, Hallström B, Hamberger B, Motawia MS, Olsen CE, Staerk D, Hansen J, Møller BL, Hamberger B. (2017). Total biosynthesis of the cyclic AMP booster forskolin from Coleus forskohlii. Elife;6:e23001. doi: 10.7554/eLife.23001. PMID: 28290983; PMCID: PMC5388535.
148. Paul A. Backman, Richard A. Sikora, (2008). Endophytes: An emerging tool for biological control, Biological Control. Volume 46, Issue 1, Pages 1-3, ISSN 1049-9644, https://doi.org/10.1016/j.biocontrol. 03.009.
149. Piatkowska-Jakubas B, Krawczyk-Kuliś M, Giebel S, Adamczyk-Cioch M, Czyz A, Lech Marańda E, Paluszewska M, Pałynyczko G, Piszcz J, Hołowiecki J. (2008). Polish Adult Leukemia Group. Use of L-asparaginase in acute lymphoblastic leukemia: recommendations of the Polish Adult Leukemia Group. Pol Arch Med Wewn.;118(11):664-9. PMID: 19140571.
150. Prashith-Kekuda TR. (2016). Isolation, characterization and antimicrobial potential of endophytic actinomycetes. Int J Curr Microbiol Appl Sci 5:100–116. doi:10.20546/ijcmas.2016.507. 008
151. Pu X, Chen F, Yang Y, Qu X, Zhang G, Luo Y. (2015). Isolation and characterization of *Paenibacillus polymyxa* LY214, a camptothecin-producing endophytic bacterium from Camptotheca acuminata. Journal of Industrial Microbiology & Biotechnology 42, 1197–1202. Pu, X., Qu, X., Chen, F., Bao, J., Zhang, G., Luo, Y., 2013. Camptothecin-producing endophytic fungus *Trichoderma atroviride* LY357: isolation, identification, and fermentation conditions optimization for camptothecin production. Applied Microbiology and Biotechnology 97, 9365–9375.
152. Pu X, Zhang C. R, Zhu L, Li Q. L, Huang Q. M, Zhang L, & Luo Y. G. (2019). Possible clues for camptothecin biosynthesis from the metabolites in camptothecin-producing plants. Fitoterapia, 134, 113–128
153. Puri S. C, Verma V, Amna T, Qazi G. N, & Spiteller M. (2005). An endophytic fungus from Nothapodytes foetida that produces Camptothecin. Journal of Natural Products, 68, 1717–1719
154. Puri SC, Nazir A, Chawla R, Arora R, Riyaz-Ul-Hasan S, Amna T, Ahmed B, Verma V, Singh S, Sagar R, Sharma A, Kumar R, Sharma RK, Qazi GN. (2006). The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans. J Biotechnol.;122(4):494-510. doi: 10.1016/j.jbiotec.2005.10.015. Epub 2005 Dec 20. PMID: 16375985.
155. Qi X, Li X, Zhao J, He N, Li Y, Zhang T, Wang S, Yu L, Xie Y. (2019). GKK1032C, a new alkaloid compound from the endophytic fungus Penicillium sp. CPCC 400817 with activity against methicillinresistant S. aureus. J Antibiot 72(4):237–240
156. Qiao W, Ling F, Yu L, Huang Y, Wang T. (2017). Enhancing taxol production in a novel endophytic fungus, *Aspergillus aculeatinus* Tax- 6, isolated from Taxus chinensis var. mairei. Fungal Biol.;121:1037–44. https://doi.org/10.1016/j.funbio.2017.08.011
157. Rahman R.A, Moamen O.A, Abdelmonem N, Ismail I.M. (2019). Optimizing the removal of strontium and cesium ions from binary solutions on magnetic nanozeolite using response surface methodology (RSM) and artificial neural network (ANN). Environmental Research 173, 397–410
158. Rai M, Rathod D, Agarkar G, Dar M, Brestic M, Pastore GM, Roberto M M J. (2014). Fungal growth promotor endophytes: a pragmatic approach towards sustainable food and agriculture. Symbiosis.; 62:63– 79. https://doi.org/10.1007/s13199-014-0273-3.
159. Ran X, Zhang G, Li S, Wang J. (2017). Characterization and antitumor activity of camptothecin from endophytic fungus *Fusarium solani* isolated from *Camptotheca acuminate*. Afr Health Sci.;17: 566–74. https://doi.org/10.4314/ahs.v17i2.34
160. Rather G.A, Sharma A, Pandith S.A, Kaul V, Nandi U, Misra P, Lattoo S.K. (2017). De novo transcriptome analyses reveals putative pathway genes involved in biosynthesis and regulation of camptothecin in *Nothapodytes nimmoniana* (Graham) Mabb. Plant Molecular Biology 96, 197–215.
161. Raveendran VV. (2015). Camptothecin-discovery, clinical perspectives and biotechnology. Nat Prod Chem Res.;3:175.
162. Remesh A. (2017). Toxicities of anticancer drugs and its management. Int. J. Basic Clin. Pharmacol. 1, 2–12. doi: 10.5455/2319-2003.ijbcp000812
163. Retna AM, Ethalsa P. (2013). A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Catharanthus roseus* (Apocyanaceae). IJERT 2(10):3899–3912
164. Rowinsky EK, Onetto N, Canetta RM, Arbuck SG. (1992). Taxol-the 1st of the texanes, an important new class of anti-tumor agents. Semin Oncol.; 19: 646-62.
165. S C, B J, Mathew J, Radhakrishnan EK. (2017). Endophytic Phomopsis sp. colonization in *Oryza sativa* was found to result in plant growth promotion and piperine production. Physiol Plant. Aug;160(4):437-446. doi: 10.1111/ppl.12556. Epub 2017 Jun 5. PMID: 28224643.
166. Salam N, Khieu TN, Liu MJ, Vu TT, Chu-Ky S, Quach NT, Phi QT, Narsing Rao MP, Fontana A, Sarter S, Li WJ. (2017). Endophytic Actinobacteria Associated with Dracaena cochinchinensis Lour.: Isolation, Diversity, and Their Cytotoxic Activities. Biomed Res Int. 2017;2017:1308563. doi: 10.1155/2017/1308563. Epub. PMID: 28484706; PMCID: PMC5397652.
167. Seehafer K, Rominger F, Helmchen G, Langhans M, Robinson DG, Özata B, Brügger B, Strating JR, van Kuppeveld FJ, Klein CD. (2013). Synthesis and biological properties of novel brefeldin A analogues. J Med Chem.;56(14):5872-84. doi: 10.1021/jm400615g. Epub 2013 Jul 8. PMID: 23805957.
168. Selim M, Elshikh H, Saad M, Mostafa E, and Mahmoud M. (2016). "Purification and characterization of a novel thermo stable L-methioninase from Streptomyces sp. DMMMH4 and its evaluation for anticancer activity," Journal of Applied Pharmaceutical Science, vol. 6, no. 7, pp. 53–60,

169. Selim M. H, Karm Eldin E. Z, Saad M. M, E. Mostafa E.S, Shetia Y. H, and A. A. H. (2015). Anise, "Purification, characterization of L-methioninase from Candida tropicalis, and its application as an anticancer," Biotechnology Research International, Article ID 173140, 10 pages,
170. Shiono Y, Kikuchi M, Koseki T, Murayama T, Kwon E, Aburai N, Kimura KI. (2011). Isopimarane diterpene glycosides, isolated from endophytic fungus Paraconiothyrium sp. MY-42. Phytochemistry 72:1400–1405
171. Shweta S, Gurumurthy BR, Ravikanth G, Ramanan US, Shivanna MB. (2013). Endophytic fungi from Miquelia dentata Bedd., produce the anti-cancer alkaloid, camptothecine. Phytomedicine.;20(3-4):337-42. doi: 10.1016/j.phymed.2012.11.015. Epub 2012 Dec 27. PMID: 23273751.
172. Shweta S, Zuehlke S, Ramesha BT, Priti V, Mohana Kumar P, Ravikanth G, Spiteller M, Vasudeva R, Uma Shaanker R. (2010) Endophytic fungal strains of Fusarium solani, from Apodytes dimidiata E. Mey. ex Arn (Icacinaceae) produce camptothecin, 10-hydroxycamptothecin and 9-methoxycamptothecin. Phytochemistry.;71(1):117-22. doi: 10.1016/j.phytochem.2009.09.030. Epub 2009 Oct 26. PMID: 19863979.
173. Silva A M M, Silva A R, Pinheiro A M, Freitas S R V B, Silva V D A, Souza C S, Hughes J B, El-Bachá R S, Costa M F D, Velozo E S, Tardy M,Costa S L. (2007). Alkaloids from *Prosopis juliflora* leaves induce glial activation, cytotoxicity and stimulate NO production. Toxicon, 49 (5): 601-614
174. Song X, Zhou X, Li X, Zheng C, Huang G, Yu Z Chen Y. Guangping. (2016). Secondary Metabolites of a *Bruguiera sexangula* var. Rhynchopetala-Derived Fungus Phomopsis longicolla HL-2232. Chinese Journal of Organic Chemistry. 35. 2102-2107. 10.6023/cjoc201505044., et al., Secondary metabolites of a Bruguiera sexangula var. Rhynchopetala derived fungus Phomopsis longicolla HL-2232. Youji Huaxue. 2015;35: 2102–7
175. Soujanya K, Siva R, Kumara P.M, Srimany, A, Ravikanth G, Mulani F.A, Aarthy T, Thulasiram H.V, Santhoshkumar T.R, Nataraja K.N, Shaanker R.U. (2017). Camptothecin-producing endophytic bacteria from *Pyrenacantha volubilis* Hook. (Icacinaceae): a possible role of a plasmid in the production of camptothecin. Phytomedicine 36, 160–167
176. Stahelin H. (1973). Activity of a new glycosidic lignan derivative (VP-16–213) related to podophyllotoxin in experimental tumors. Eur J Cancer 9:215–221.
177. Stierle A, Strobel G, Stierle D. (1993). Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew. Science; 260:214–216.
178. Stojanovi´c-Radi´c Z, Pej˘ci´c M, Dimitrijevi´c M, Aleksi´c A, Anil Kumar N.V, Salehi B, Cho W.C, Sharifi-Rad J. (2019). Piperine-A Major Principle of Black Pepper: A review of its bioactivity and studies. Appl. Sci., 9, 4270. [CrossRef]
179. Strobel G, Daisy B, Castillo U, Harper J (2004) Natural products from endophytic microorganisms. J Nat Prod 67(2):257– 268. https://doi.org/10.1021/np030397v
180. Sun X, Cui M, Wang D, Guo B, & Zhang L. (2018). Tumor necrosis factor-related apoptosis inducing ligand overexpression and Taxol treatment suppresses the growth of cervical cancer cells in vitro and in vivo. Oncology Letters, 15, 5744–5750
181. Swamy MK, Akhtar MS, Sinniah UR. (2016). Response of PGPR and AM Fungi toward growth and secondary metabolite production in medicinal and aromatic plants. In: Hakeem KR, Akhtar MS (eds) Plant, soil and microbes: mechanisms and molecular interactions. Springer International Publishing, Cham, pp 145–168
182. Takimoto C. H. (2002). Camptothecins A2 - Bertino, Joseph R, in Encyclopedia of Cancer, 2nd Edn., ed Bertino J. (New York, NY: Academic Press;), 301–309. [Google Scholar]
183. Tan RX, Zhou WX. (2001). Endophytes: a rich source of functional metabolites. Nat Prod Rep 18:448–459
184. Tan X, Zhou Y, Zhou X, Xia X, Wei Y, He L, & Yu. (2018). Diversity and bioactive potential of culturable fungal endophytes of Dysosma versipellis; A rare medicinal plant endemic to China. Scientifc Reports, 8, 1–9
185. Tang J.W, Kong L.M, Zu W.Y, Hu K, Li X.N, Yan B.C, Wang W.G, Sun H.D, Li Y, Puno P.T, Isopenicins A.C. (2019). Two types of antitumor meroterpenoids from the plant endophytic fungus Penicillium sp. sh18. Org. Lett. 21, 771–775. https://doi.org/10.1021/acs.orglett.8b04020.
186. Thirumara, R, Prendergast G. C, & Gilman P. B. (2007). Cytotoxic chemotherapy in clinical treatment of cancer. Cancer Immunotherapy (pp. 101–116). Elsevier
187. Trapp MA, Kai M, Mithofer A, Rodrigues-Filho E. (2015). Antibiotic oxylipins from *Alternanthera brasiliana* and its endophytic bacteria. Phytochemistry 110:72–82
188. Turbyville TJ, Kithsiri Wijeratne EM, Liu MX, Burns AM, Seliga CJ, Luevano LA, David CL, Faeth SH, Whitesell L, Gunatilaka AAL. (2006). Search for Hsp90 inhibitors with potential anticancer activity: isolation and SAR studies of radicicol and monocillin i from two plant-associated fungi of the sonoran deser. J Nat Prod 69:178–184
189. Tyagi G, Kapoor N, Chandra G, Gambhir L. (2021). Cure lies in nature: medicinal plants and endophytic fungi in curbing cancer. 3 Biotech. 2021 Jun;11(6):263. doi: 10.1007/s13205-021-02803-x. Epub PMID: 33996375; PMCID: PMC8116431.
190. Ulukan H, and Swaan P. W. (2002). Camptothecins. Drugs 62, 2039–2057. doi: 10.2165/00003495-200262140-00004.
191. Utsugi T, Shibata J, Sugimoto Y, Aoyagi K, Wierzba K, Kobunai T, Terada T, Oh-hara T, Tsuruo T, Yamada Y. (1996). Antitumor activity of a novel podophyllotoxin derivative (TOP-53) against lung cancer and lung metastatic cancer. Cancer Res.;56(12):2809-14. PMID: 8665518.
192. Uzma F, Mohan CD, Hashem A, Konappa NM, Rangappa S, Kamath PV, Singh BP, Mudili V, Gupta VK, Siddaiah CN, Chowdappa S, Alqarawi AA, Abd Allah EF. (2018). Endophytic Fungi-Alternative Sources of Cytotoxic Compounds: A Review. Front Pharmacol.;9:309. doi: 10.3389/fphar.2018.00309. PMID: 29755344; PMCID: PMC5932204.
193. Venugopalan A, Potunuru U.R, Dixit M, Srivastava S. (2016). Reprint of: effect of fermentation parameters, elicitors and precursors on camptothecin production from the endophyte Fusarium solani. Bioresource Technology 213, 311–318.
194. Venugopalan A, Srivastava S. (2015). Endophytes as in vitro production platforms of high value plant secondary metabolites. Biotechnol Adv.;33:873–87. https://doi.org/10.1016/j.biotechadv.2015. 07.004.
195. Verma V.C, Lobkovsky E, Gange A.C, Singh S.K. Prakash S. (2011). Piperine production by endophytic fungus Periconia sp. isolated from Piper longum L. J. Antibiot., 64, 427–431. [CrossRef] 61.
196. Wall ME, Wani MC. (1996). Camptothecin and taxol: from discovery to clinic. J Ethnopharmacol. (1-3):239-53; discussion 253-4. doi: 10.1016/0378-8741(95)01367-9. PMID: 9213622.
197. Wang J, Huang Y, Fang M, Zhang Y, Zheng Z, Zhao Y, Su W. (2002). Brefeldin A, a cytotoxin produced by Paecilomyces sp. and Aspergillus clavatus isolated from Taxus mairei and Torreya grandis. FEMS Immunol Med Microbiol 34:51–57
198. Wang j. Y. Huang M, Fang Y, Zhang Z, Zheng Y, Zhao and W. Su. (2002). FEMS Immunol. Med. Microbiol, 34, 51–57.
199. Wang Q, Fu Y, Gao J, Wang Y, Li X. Zhang A. (2007). Preliminary isolation and screening of the endophytic fungi from Melia azedarach L. Acta Agric. Boreali-Occident. Sin., 16, 224–227.
200. Wang QX, Li SF, Zhao F, Dai HQ, Bao L, Ding R, Gao H, Zhang LX, Wen HA, Liu HW. (2011). Chemical constituents from endophytic fungus *Fusarium oxysporum*. Fitoterapia. 2011 Jul;82(5):777-81. doi: 10.1016/j.fitote.2011.04.002. Epub. PMID: 21497643.

201. Wang T, Ma Y, Ye Y, Zheng H, Zhang B, & Zhang E. (2017). Screening and identifcation of endophytic fungi producing podophyllotoxin compounds in *Sinopodophyllum hexandrum* stems. Chinese J Exp Trad Med Formul, 18, 493–532.
202. Wang Y, Dai CC. (2011). Endophytes: a potential resource for biosynthesis, biotransformation, and biodegradation. Ann Microbiol 61:207–215
203. Wang Y, Ma Z, Hu F, Fan M, Li Z. (2014). Isolation and screening of endophytic fungi producing taxol from Taxus chinensis of Huangshan. Nat. Prod. Res. Dev., 26, 1624–1627
204. Wang, M., Sun, Z.H., Chen, Y.C., Liu, H.X., Li, H.H., Tan, G.H., Li, S.N., Guo, X.L., Zhang, W.M., 2016. Cytotoxic cochlioquinone derivatives from the endophytic fungus *Bipolaris sorokiniana* derived from *Pogostemon cablin*. Fitoterapia 110, 77–82. https://doi.org/10.1016/j.fitote.2016.02.005.
205. Wani MC, Horwitz SB. (2014). Nature as a remarkable chemist: a personal story of the discovery and development of Taxol. Anticancer Drugs.;25(5):482-7. doi: 10.1097/CAD.0000000000000063. PMID: 24413390; PMCID: PMC3980006.
206. Wani MC, Taylor HL, Wall ME, Coggon P, Mcphail AT. (1971). Plant antitumor agents.VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from taxus brevifolia2. J Am Chem Soc 93(9):2325–2327. https://doi.org/10.1021/ja007 38a045
207. Wheeler NC, Jech K, Masters S, Brobst SW, Alvarado AB, Hoover AJ, Snader KM. (1992). Effects of genetic, epigenetic, and environmental factors on taxol content in *Taxus brevifolia* and related species. J Nat Prod.;55(4):432-40. doi: 10.1021/np50082a005. PMID: 1355111.
208. Wijeratne EM, Bashyal BP, Liu MX, Rocha DD, Gunaherath GM, U'Ren JM, Gunatilaka MK, Arnold AE, Whitesell L, Gunatilaka AA. (2012). Geopyxins A-E, ent-kaurane diterpenoids from endolichenic fungal strains Geopyxis aff. majalis and Geopyxis sp. AZ0066: structure-activity relationships of geopyxins and their analogues. J Nat Prod.;75(3):361-9. doi: 10.1021/np200769q. Epub. PMID: 22264149; PMCID: PMC3359839.
209. Wink M, Alfermann A. Franke, Rochus W, Bernhard D, Melanie W, Jörg K, Oliver F, Elisabeth G, Hermann M, Abdolali W, Eckart R, Peter. (2005). Sustainable bioproduction of phytochemicals by plant in vitro cultures: Anticancer agents. Plant Genetic Resources: Characterization and Utilization. 3. 90 - 100. 10.1079/PGR200575Wink M et al (2005) Sustainable bioproduction of phytochemicals by plant in vitro cultures: anticancer agents. Plant Genet Resour 3(2):90–100. https://doi.org/10.1079/pgr200575
210. Woodrow CJ, Haynes RK, Krishna S. (2005). Artemisinins. Postgrad Med J. Feb;81(952):71-8. doi: 10.1136/pgmj.2004.028399. PMID: 15701735; PMCID: PMC1743191.
211. Wrasidlo W, Gaedicke G, Guy RK, Renaud J, Pitsinos E, Nicolaou KC, Reisfeld RA, Lode HN. (2002). A novel 2'-(N-methylpyridinium acetate) prodrug of paclitaxel induces superior antitumor responses in preclinical cancer models. Bioconjug Chem.;13(5):1093-9. doi: 10.1021/bc0200226. PMID: 12236791.
212. Wu LS, Hu CL, Han T, Zheng CJ, Ma XQ, Rahman K, Qin LP. (2013). Jan Cytotoxic metabolites from Perenniporia tephropora, an endophytic fungus from Taxus chinensis var. mairei. Appl Microbiol Biotechnol.;97(1):305-15. doi: 10.1007/s00253-012-4189-7. Epub 2012 Jun 3. PMID: 22660771.
213. Wu YY, Lu CH, Qian XM, Huang YJ, Shen YM. (2009). Diversities within genotypes, bioactivity and biosynthetic genes of endophytic actinomycetes isolated from three pharmaceutical plants. Curr Microbiol; 59:475-482.
214. Wu ZC, Li DL, Chen YC, Zhang WM. (2010). A new isofuranonaphthalenone and Benzopyrans from the endophytic fungus Nodulisporium sp. A4 from Aquilaria sinensis. Helv Chim Acta 93:920–924
215. Xie F, Li X. B, Zhou J. C, Xu Q. Q, Wang X. N, Yuan H. Q, & Lou H. X. (2015). Secondary metabolites from Aspergillus fumigatus, an endophytic fungus from the liverwort *Heteroscyphus tener* (Steph.) Schifn. Chemistry Biodiversity, 12, 1313–1321
216. Xin X.Q, Chen Y, Zhang H, Li Y, Yang M.H, Kong L.Y. (2019). Cytotoxic secocytochalasins from an endophytic Aspergillus sp. harbored in Pinellia ternata tubers. Fitoterapia 132, 53–59. https://doi.org/10.1016/j.fitote.2018.11.010.
217. Xue L, Xue Q, Chen Q, Lin C, Shen G, Zhao J. (2013). Isolation and evaluation of rhizosphere actinomycetes with potential application for biocontrol of Verticillium wilt of cotton. Crop Prot 43:231–24
218. Yamada Y, Kuzuyama T, Komatsu M, Shin-Ya K, Omura S, Cane DE, Ikeda H. (2015). Terpene synthases are widely distributed in bacteria. Proc Natl Acad Sci U S A.;112(3):857-62. doi: 10.1073/pnas.1422108112. Epub 2014 Dec 22. PMID: 25535391; PMCID: PMC4311827.
219. Yang X-L, Li Z-Z. (2013). New spiral γ-lactone enantiomers from the plant endophytic fungus *Pestalotiopsis foedan*. Molecules; 18(2): 2236-42. X-L, Li Z-Z. New spiral γ-lactone enantiomers from the plant endophytic fungus *Pestalotiopsis foedan*. Molecules 2013; 18(2): 2236-42.
220. Yang Y, Zhao H, Barrero RA, Zhang B, Sun G, Wilson IW, Xie F, Walker KD, Parks JW, Bruce R, Guo G, Chen L, Zhang Y, Huang X, Tang Q, Liu H, Bellgard MI, Qiu D, Lai J, Hoffman A. (2014). Genome sequencing and analysis of the paclitaxel-producing endophytic fungus *Penicillium aurantiogriseum* NRRL 62431. BMC Genomics.;15:69. doi: 10.1186/1471-2164-15-69. PMID: 24460898; PMCID: PMC3925984.
221. Ying YM, Shan WG, Zhang LW, Zhan ZJ. (2013). Ceriponols A–K, tremulane sesquitepenes from Ceriporia lacerate HS-ZJUTC13A, a fungal endophyte of *Huperzia serrata*. Phytochemistry 95:360–367
222. Yu M N. H, Kim J. A, Jeong M. H, Cheong Y. H, Hong S. G, Jung J. S Young Jin K Hur J. S. (2014). Diversity of endophytic fungi associated with bryophyte in the maritime Antarctic (King George Island). Polar Biology, 37, 27–36
223. Yuan Z, Tian Y, He F, Zhou H. (2019). Endophytes from *Ginkgo biloba* and their secondary metabolites. Chin Med 14:51. https://doi. org/10.1186/s13020-019-0271-8
224. Yun, J., Pannuti, A., Espinoza, I. H Zhu, C Hicks, X Zhu, M Caskey, P Rizzo, G D'Souza, K Backus, M F Denning, J Coon, M Sun, E H Bresnick, C Osipo, J Wu, P R Strack, D A Tonetti & L Miele. (2013). Crosstalk between PKCα and Notch-4 in endocrine-resistant breast cancer cells. Oncogenesis 2, e60 https://doi.org/10.1038/oncsis.2013.26
225. Zaiyou J, Li M, Xiqiao H. (2017). An endophytic fungus efficiently producing paclitaxel isolated from *Taxus wallichiana* var. mairei. Medicine.;96:e7406. https://doi.org/10.1097/MD. 0000000000007406.
226. Zeng Q, Huang H, Zhu J, Fang Z, Sun Q, Bao S. (2013). A new nematicidal compound produced by *Streptomyces albogriseolus* HA10002. Antonie Van Leeuwenhoek 103:1107–1111
227. Zhan J, Burns AM, Liu MX, Faeth SH, Gunatilaka AAL. (2007). Search for cell motility and angiogenesis inhibitors with potential anticancer activity: beauvericin and other constituents of two endophytic strains of *Fusarium oxysporum*. J Nat Prod 70:227–232.
228. zhang L, Bo G, Li H, Songrong Z, Hua S, Su G, & Wei R. (2000). Preliminary Study on the Isolation of Endophytic Fungus of *Catharanthus roseus* and Its Fermentation to Produce Products of Therapeutic Value. Chinese Traditional and Herbal Drugs, 31, 805-807.
229. Zhang S, Cao L, Wang Z, Li Z, Ma J. (2019). Anti-cancer effect of toosendanin and its underlying mechanisms. J. Asian Nat. Prod. Res., 21, 270–283. [CrossRef]
230. Zhang W, Xu L, Yang L, Huang Y, Li S, Shen Y. (2014). Phomopsidone A, a novel depsidone metabolite from the mangrove endophytic fungus Phomopsis sp. A123. Fitoterapia; 96: 146-51.

231. Zhao J, Zhou L, Wang J, Shan T, Zhong L, Liu X, & Gao X.Y. (2010). Endophytic fungi for producing bioactive compounds originally from their host plants.
232. Zhao K, Yu L, Jin Y, Ma X, Liu D, & Wang X. (2016). Advances and prospects of taxol biosynthesis by endophytic fungi. Chinese Journal of Biotechnology, 32, 1038–1051.
233. Zheng J, Zhou Y, Li Y, Xu DP, Li S, Bin Li H. (2016). Spices for prevention and treatment of cancers. Nutrients 8:495. https://doi.org/10.3390/nu8080495
234. Zhou JY, Yuan J, Li X, Ning YF, Dai CC. (2015). Endophytic bacterium triggered reactive oxygen species directly increase oxygenous sesquiterpenoid content and diversity in *Atractylodes lancea*. Appl Environ Microbiol 82:1577–1585
235. Zhou P, Wu Z, Tan D, Yang J, Zhou Q, Zeng F, Zhang M, Bie Q, Chen C, Xue Y, Luo Z, Wang J, Zhu H, Zhang Y. (2017). Atrichodermones A–C, three new secondary metabolites from the solid culture of an endophytic fungal strain, *Trichoderma atroviride.* Fitoterapia 123: 18–22