Endophytes as source of anticancer drugs

Ayana K K[1] and M. Anilkumar[2]

Cell culture Lab, Research Department of Botany, Union Christian College, Aluva, Ernakulam

Pin – 683102, Kerala, India

Email: [1]ayanapottassery@gmail.com ; [2]drmakumar@gmail.com

Contents

ABSTRACT

Cancer is the loss of control over cell division, apoptotic resistance and invasion into normal tissue and forms one of the most important causes of death. 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 plants 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. Anticancer agents. Host plant. Secondary metabolites.

I. INTRODUCTION

Cancer is the uncontrolled growth of cells which eventually invade adjacent tissues and spread to other organs and finally 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 cancer to other body parts is termed metastasis and is the major cause of death by cancer. There are hundreds of distinct types of cancer that vary in their behaviour and response to treatment. Exposure to hundreds of carcinogens has created an exponential rise in the world population with a variety of health issues including cancer (Chakravarty and Gaur 2018). The present therapeutic regime against cancer is facing many challenges including the emergence of chemoresistance and deterioration of health after a period of treatment. In this context, the investigation into new therapeutic drugs and their underlying mechanism of action is of immense help to humanity (Tyagi et al., 2021). Hence, alternative methods for cancer treatment with lesser side effects are the need of the hour. Even though many phytochemicals were identified as potential sources of anticancer drugs, their applications in the drug research pipeline have recently declined. 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 associated with the use of plants as the source of drugs include slow growth rate taking several years for product accumulation and extraction, overexploitation that leads to the vulnerability of plant species and inconsistency of the phytochemical produced by the plant source (Kala et al., 2006). Many endophytes have been identified from different plant species from different geographical areas with diverse climatic conditions (Arora and Ramawat 2017). Microorganisms can be considered the best source of inexhaustible, easily renewable and prolific sources 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).

Many endophytes have been identified 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 which in turn determines the extent of colonization (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). The type of active compounds produced by endophytes can be more than those produced by host plants (Wang and Dai 2011). Endophytes colonise plant tissues without producing any disease symptoms effects (Bacon and White 2016). The secondary metabolites isolated from endophytes show a wide range of bioactivities such as antibacterial, antifungal and anticancer (Jalgaonwala et al., 2017). Based on morphological characters and molecular profiling by intergenic transcribed spacer (ITS) sequences, the endophytic microbes are categorised as endophytic bacteria, endophytic fungi and endophytic actinomycetes. The fungal endophytes reside in the host plants without showing any disease indication when compared to their pathogenic counterparts (Swamy et al., 2016). Antibacterial, antiviral, antitumour, anti-inflammatory and immunostimulatory properties have been reported from fungal endophytes (Bedi et al., 2017; Mishra et al., 2011). So far, less than 16% of the fungal species described have been cultured and studied in detail. Fungal species richness is estimated to be around 2.2 to 3.8 million globally (Hawksworth and Lücking 2017) of which less than 5% represent a large source of characteristic bioactive metabolites (Bedi et al., 2018).

Among the available anti-cancer drugs, many of them show toxicity towards normal proliferating cells and cause unpropitious effects. They are ineffective against distinct types of cancer which results in the need for other natural phytochemicals of therapeutic value (Remesh, 2017). A broad range of bioactive molecules such as alkaloids, terpenoids, quinones, flavonoids, 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-based anticancer drugs such as taxol, vinblastine, vincristine, etoposide, topotecan etc (Balunas and Kinghorn, 2005). In this chapter, we also describe the novel secondary metabolites used as anti-cancer drugs produced by fungal endophytes, cytotoxicity towards particular cancer cell lines and the interaction between microbes and hosts along with the structure of some major anticancer compounds. The purpose of this chapter is to highlight a recent line of investigation into the possibility of developing anticancer medications from fungal endophytes that produce potential anticancer chemicals. The purpose of this chapter is to highlight a recent line of investigation into the possibility of developing anticancer drugs from fungal endophytes that are capable of producing potential anticancer chemicals.

II. ENDOPHYTIC ACTINOMYCETES

Actinomycetes of various genera associated with various parts of plants are termed endophytic actinomycetes. They form one of the most relevant sources of novel phytochemicals having many pharmaceutical and agricultural values. A wide range of bioactivities such as antiviral, anti-cancer, antimicrobial and antioxidant activities are shown by the crude extracts as well as by the purified compounds from endophytic actinomycetes. (Prashith Kekuda 2016). It was reported that more than 50,000 bioactive secondary metabolites were produced by actinomycetes. Comparatively, a smaller number of endophytes were reported from medicinal plants than those from soil and marine sources (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). Because endophytic extracts are more effective at triggering the antitumor response and have fewer adverse effects, 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 contain glucanase, which can both stimulate plant growth and prevent *Pythium aphanidermatum* growth (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 culture medium extract of Streptomyces sp. BO-07 had antibacterial activity against Gram-positive bacteria and antioxidant and strong anticancer actions (Taechowisan et al., 2017)

III. BACTERIAL ENDOPHYTES AS A SOURCE OF ANI-CANCER DRUGS

The favourable benefits of bacterial endophytes comprise increased biological N2 fixation, phosphate solubilization, suppression of ethylene biosynthesis in response to stressors, generation of phytohormones, and 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-culture of microorganisms is another name for co-cultivation. That is for instance culture of two bacterial or fungal strains subjugated for large-scale production of desired metabolites (Bertrand et al., 2014). Two distinctive derivatives of 3,4-dihydronaphthalen-(2 H)-1-one (1-tetralone) are produced when the bacteria *Bacillus subtilis* 168 trpC2 and endophytic fungus Aspergillus versicolor KU258497 are co-cultured. One product, aspvanicin B, exhibits notable cytotoxicity towards the mouse lymphoma cell line L5178Y (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 attained from their endophytic bacterial part (Trapp et al., 2015). From a kind of *Dracaena cochinchinensis* Lour tissues (Dragon's blood, a traditional Chinese medicine, is made), 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 Hep G2, human cancer cell lines and MCF-7 (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. Increased plant growth and ginsenoside content were noticed 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. L-Asparaginase was added to the multi-drug treatment in children and adults with acute lymphoblastic leukemia, and the majority of patients exhibited improvement and full remission (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 outlining of *Pseudomonas cichorii*, *Arthrobacter pascens* and *Bacillus safensis* disclosed the occurrence 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 bioprospecting for 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).

IV. 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, concerning cytotoxic and antibacterial potential, endophytic extracts were tested. In response to this, over 72% of the extract showed cytotoxic action contrary to one of the analyzed cell lines, and 39% of the extracts exhibited >50% inhibited growth against all of the tested cell lines (Katoch et al., 2017). Fungal endophytic of *Cupressus torulosa* (*Pestalotiopsis neglecta*BAB-5510) is considered one of the promising sources of alkaloids, saponin, tannins, terpenoids, flavonoids, 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. By turning on several latent biogenetic gene clusters in the fungus, this crucial tool can possibly be utilised to produce metabolites in huge quantities, either of the same or different kinds. (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 (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).

Red and chilli peppers contain the bioactive chemical capsaicin, which is utilized as a painkiller and an anticancer treatment for numerous types of human tumours. Capsaicin is produced by the endophytic fungus *Alternaria alternata*, which is secluded from *Capsicum annum* (Devari et al., 2014; Clark and Lee 2016). According to a different investigation, endophytic fungi with the potential to be the source of podophyllotoxin, including *Juniperus communis* L., Horstmann, *Phialocephala fortinii*, and *Trametes hirsuta*, were secluded from plants with anticancer potential, including *Podophyllum peltatum* and *Juniperus recurve* (Ardalani et al., 2017). Three mellenin derivatives isolated from the *Penicillium sp*. from Senecio favus 5-methylmellein (18), 6-hydroxymellein (19), and 4-hydroxymellein (20), IC50 values of >10 mg/mL, 6.1 mg/mL, and 8.3 mg/mL, respectively, indicated cytotoxicity against the MCF-7 cancer cell line (Elkhayat and Goda 2017). A chiral isomer of cladosporol A called alterfungin has anticancer efficacy in mice receiving stomach 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 cell line (A549), multiple drug resistance PC3D cells, human prostate cancers PC3, human lung adenocarcinoma epithelial and human lung cancer cell line (NCI-H460) (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).

V. 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, medicinal plants' endophytes emulate the synthesis of bioactive substances and exhibit anti-malarial, anti-cancer and antioxidant pharmacological actions (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)

Secondary metabolites produced by fungi endophytes that are biologically active comprise flavonoids, terpenoids, phenolic acids, steroids, alkaloids, quinones, benzopyranones, chinones, tetralones, xanthones etc. (Tan and Zhou 2001; Swamy et al., 2016). The milestone for the exploration of natural

secondary metabolites from endophytes begins with the identification of *Taxomyces andreanae*, a taxol-producing fungus, in the Pacific yew *Taxus brevifolia* (Stierle et al., 1993). The CHCl3 extract of *Pantoea agglomerans* from Prunella vulgaris, for instance, demonstrated strong action against the liver cancer cell line HepG2 with an IC50 of 0.12 g/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 to ascertain its effectiveness with different cell lines, several cancer cell lines might be utilized (Farias et al., 2019).

A. Taxol (Paclitaxel)

For the first time, taxol was procured from the bark of *Taxus brevifolia*, which is a potential bioactive compound marketed under the name Taxol (Wani et al., 1971). Other than *Taxus brevifolia* various 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 the early 1960s and later it turned out as the world's first billion-dollar anticancer drug, belonging to the class of taxanes that is vastly 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 is augmented with certain advantageous elements such as precursors, carbon sources, metabolic bypass inhibitors, inducers, and nitrogen sources along with an optimized culture parameter, will result in a higher 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, it is possible to separate Baccatin III and 10-deacetylbaccatin III, which resemble late precursors of Taxol, out of 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, it was previously shown in a report that the administration of benzoic acid stimulated the formation of taxol by the fungus *Periconia* sp. linked with *Torreya grandifolia*. 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 optimized because the generation of Taxol via endophytic fungi wasn't steady 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 woof equivalent 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 team of scientists during *Penicillium aurantiogriseum* NRRL (a fungal endophyte) genome sequence analysis (Yang et al., 2014).

Usually, paclitaxel action involves the binding of paclitaxel with the protein tubulin 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). Cancers include non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, AIDS-related Kaposi sarcoma, and AIDS-related Kaposi sarcoma can all be treated with paclitaxel alone or in conjunction with other anticancer therapies. 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). In 1992, the US FDA authorized Taxol (paclitaxel) for the curative purposes of ovarian cancer., 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* produces 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). Several species from endophytic genera are suitable for the production of Taxol,

including *Botryodiplodia theobromae, Periconia sp., Bartalinia robillardoides, Alternaria alternata, Pithomyces sp., Monochaetia sp., Seimatoantlerium nepalense* and *Chaetomella raphiger* (Kumar et al., 2017).

Apart from cell cycle arrest, paclitaxel has an anti-cancer effect by targeting the mitochondria, apoptosis inhibitor proteins such as B-cell Leukemia 2 (Bcl-2) and immune cells. (Ferlini, et al., 2003) Angiogenesis is an important feature of cancer cells. According to previous studies, Bcl-2's expression is being decreased, whereas DR5 and cleaved caspase-3's expression are being increased. In metastatic cervical carcinoma, paclitaxel improves the effects of tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) (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 (VEGF) vascular endothelial growth factor expression 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 techniques, like fast atom bombardment, immunological methods (using monoclonal antibodies specific for paclitaxel), thin layer chromatography, spectroscopy (Matrix-assisted laser desorption/ionization—Time of flight [MALDI-TOF]), high-performance liquid chromatography, and nuclear magnetic resonance [NMR]), are used to find paclitaxel in endophytes extracts. (Flores Bustamante et al., 2010).

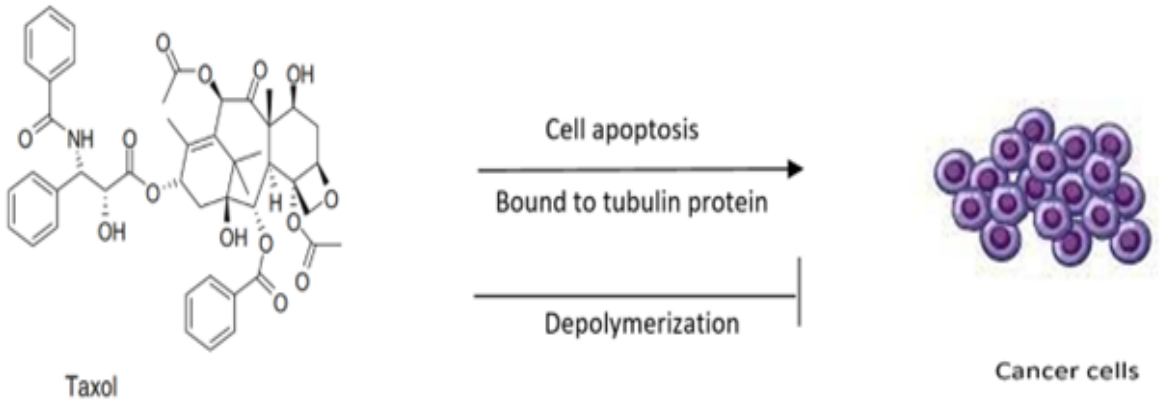


Figure: 1

B. Podophyllotoxin

Podophyllotoxin is a member of the chemical class lignans. They are pharmaceutically active natural drugs, used as precursors of antitumor drug synthesis. Some important anti-tumor medications include teniposide (VM-26) and etoposide (VP-16-213) use podophyllotoxin as their precursor molecule, these medications are used to treat various leukaemias, solid tumours, and cancers of the testicles, lungs, and other organs. (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). *Chaetomium globosum* strain MF564 of the Ascomycota division and *Pseudallescheria s*p. T55 are two further examples of fungi that produce podophyllotoxin. (Wang et al., 2017). However, because of the low abundance of plants that produce podophyllotoxin, the availability of their derivatives from conventional sources was similarly constrained. In order to increase the synthesis of substances associated with podophyllotoxin, alternative strategies like plant tissue culture were used, sustainable and reliable strategies for the production of plant-origin natural compounds (Ochoa-Villarreal et al., 2016). *WB5121 Fusarium* Strain Linked to *Dysosma Versipellis* was reported for the seclusion of podophyllotoxin with a peak yield of 277 µg/g of dry-weight mycelia (Tan et al., 2017). Fungal endophytes such as *Phialocephala fortinii*, *Juniperus communis* L. Horstmann, and *Trametes hirsuta*, 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, the dry mass

of mycelia by the fungus JRE1 *Fusarium oxysporum*, from *Juniprerus recurva*, is around 28.8 g/g (Kour et al., 2008).

Gymnosperm and angiosperm plants both produce podophyllotoxin with cancer-preventing abilities, 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. Podophyllotoxin is produced by the endophytic fungus *Fusarium solani* and is derived from the root plant *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 that backs this up mentions a strain of *Fusarium solani* that produces 29.0 g/g of podophyllotoxin in support of this describes a strain of *Fusarium solani* yielding 29.0 µg/g podophyllotoxin (Nadeem et al., 2012). Podophyllotoxin-producing endophyte, *Alternaria tenuissima* is seen as associated with *Sinopodophyllum emodi* L. root (Liang et al., 2016). The discovery of the mechanism by which fungal endophytes produce secondary metabolites was a tremendous one that led to the biological and commercial sectors. Fungal culture can be clambered up for the sufficient amount 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 podophyllotoxin called 4′-O-demethyl-4β-[(4-hydroxymethyl)-1,2,3-triazol-1-yl]-4-desoxypodophyllotoxin cyclopentyl can induce cell cycle detention at G2/M phase, apoptosis, inhibits microtubule formation, and inhibits DNA topoisomerase II. Some other promising cytotoxic activities are shown by the derivative of carbamate 4β-(1,2,3- triazol-1-yl) podophyllotoxin against cancer lines, human lung adenocarcinoma cells (A549), HeLa cells, human colon carcinoma cells (HCT-8) 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; Feher and Schmidt 2003). The antineoplastic property of Etoposide and teniposide was a result of their interaction with the enzyme topoisomerase II (Cortés and Pastor, 2003). At the Xinglong Mountains, Gansu Province, China fungal endophyte Alternaria *tenuissima* was isolated from the young roots of *Sinopodophyllum emodi* (Wall.) Ying. *Alternaria tenuissima* was known to produce podophyllotoxin, which is 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* allied 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).

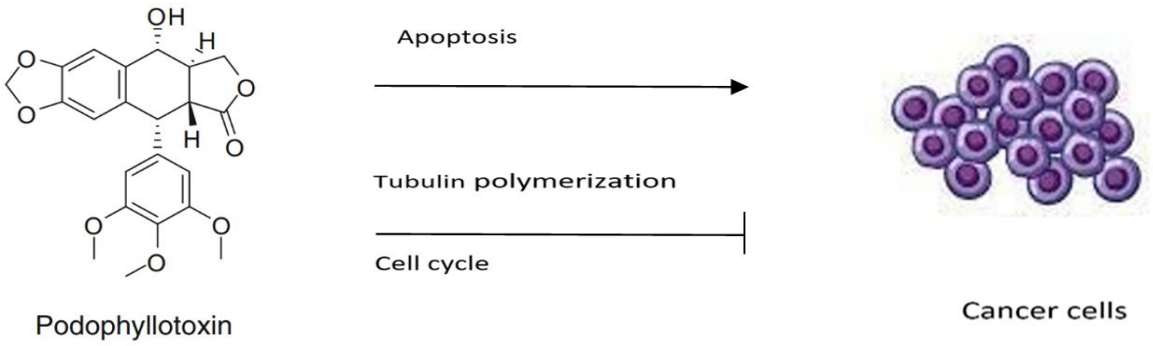


Figure: 2

There are two mechanisms by which topoisomerase inhibitors impart their function one is by the elimination of catalytic activity and the second involves raising the concentrations of DNA covalent complexes, also known as topoisomerase II poisons, in the body (Nitiss, 2009). The antimitotic activity of podophyllotoxin affects the cells by preventing tubulin polymerization, this will cause the cell cycle to be stopped at the mitotic stage and cause the production 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 death of epithelial cells is caused by the cell cycle arrest in the early metaphase stage, by blocking microtubule polymerization, the mitosis-related proteins BIRC5 and aurora B buildup cause mitotic arrest (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 starts a stress signalling cascade in the endoplasmic reticulum that promotes apoptosis. It starts a stress signalling cascade in

the endoplasmic reticulum that promotes apoptosis. 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). Epipodophyllotoxin is an active antitumor agent and isomer of podophyllotoxin, which was secluded from the roots of podophyllum species, *Podophyllum peltatum* Linnaeus and *Podophyllum emodi* Wallich (Berberidaceae) (Stahelin, 1973)

C. Camptothecin

Camptothecin is a water-insoluble compound. Which is used as an important anticancer substance used in cancer treatment and commonly generated by plants. The compound is currently approved against cancer and acts as a promising anticancer agent, a potent antineoplastic agent. It's a pentacyclic pyrroloquinoline alkaloid that's utilized to make anti-cancer medication, in the form of irinotecan and topotecan. Mostly camptothecin was secluded from *Nothapodytes foetida and Camptotheca acuminata* and it is the third largest drug that is used in cancer treatment (Demain and Vaishnav 2011). To maximize the synthesis of bioactive phytochemicals in various endophytes, several parameters including mathematical designs [response surface methodology (RSM) and artificial neural network (ANN)], bioreactor optimizations, metabolic engineering methods, etc., were employed. In recent years, RS effectively optimized one or more response factors in medicinal plants (Rahman et al., 2019; Kaur et al., 2019). The crucial step in the screening of fungal endophytes is the selection of culture media. The most often used medium for culturing fungal isolates from CPT-producing plants is potato dextrose medium (PDA/ PDB) (Musavi et al., 2015; Venugopalan et al., 2016).

At first in 1966, campothecin was acquired from *Camptotheca acuminata*'s bark (a strong anticancer quinoline indole alkaloid), but it was also found in plants including *Miquelia dentata*, *Nothapodytes nimmoniana*, and Ophiorrhiza (Wall and Wani 1996). Monoterpenoid indole, in the final stages of their production, numerous enzymatic processes convert a seco-iridoid and an indole moiety into alkaloids, they are bioactive compounds belonging to multistep biosynthetic pathways (Rather et al., 2017). They specifically target the intranuclear enzyme DNA topoisomerase I (Top 1), which keeps DNA flexible and relaxed during DNA replication and transcription., 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 habitual cells and additionally, this enzyme plays a key part in the mechanism of cancer cell replication (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 beginning of a set of events known as apoptosis, which will eventually result in cell death (Raveendran 2015). These alkaloids target only topoisomerase I apparently and their derivatives stand out for a variety of reasons. In the case of yeast cells that lacked Topoisomerase I, the cytotoxic effects of CPT had no effect on them (Bjornsti et al., 1989). There are two enantiomeric forms of camptothecin found in nature: 20-S camptothecin and 20-R camptothecin (Uzma et al., 2018). Camptothecin inhibits topoisomerase I by inhibiting the topo-1 cleavage's rejoining step, which produces an intermediate covalent reaction and the cleavable complex. They largely kill cells in the S-phase by potentially fatal collisions between advancing replication forks and cleavable topo-I complexes, and the cytotoxicity of CPT was caused by the development of long-lived topo-I DNA complexes by collisions with the transcription apparatus. (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 researches going on right now to create new techniques and methods for making camptothecin from various endophytic fungi. *Nothapodytes foetida* inner bark inhabiting fungus *Entrophospora infrequens*, was grown for maximum production of camptothecin in an optimal condition with various nutritional combinations, either by themselves or in conjunction with various sources of nitrogen and carbon (Amna et al., 2006). Two camptothecins, topotecan (fig: 3) and irinotecan (fig: 4) were authorized by the FDA for the treatment of colorectal cancer, small-cell lung cancer, and ovarian cancer about 40 years after the discovery of *C. acuminata* extract's anticancer efficacy. (Blagosklonny 2004).

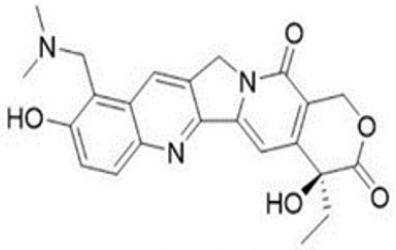


Figure 3: Topotecan

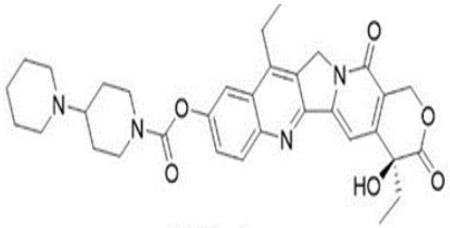


Figure 4: Irinotecan

Other than *Camptotheca acuminata* another seven families produce Camptothecin they are Piperaceae (*Piper betel*), Violaceae (*Rinorea anguifera*), Gelsemiaceae (Mostueabrunonis), Rubiaceae (*Ophiorrhiza alata, Ixora coccinea*), Apocynaceae (*Ervatamia heyneana* and *Chonemorpha fragrans*), Betulaceae (*Alnus nepalensis*) and Meliaceae (*Dysoxylum binectariferum*) (Zhang et al., 2019). In 2nd generation about .8 mg/l CPT was obtained from the endophytic bacterium *Paenibacillus polymyxa* (LY214) isolated from *Camptotheca acuminata*, which declined persistently up to 0.8 mg/l at the 8th stage (Pu et al., 2015). Recently waning of the composite's natural supplies due to low yield has emerged in Asia, because of a massive harvest of the trees that produce camptothecin to the surge in demand for it happened recently (Nadeem et al., 2012). Consequently, there occurs an imperative demand to ascertain a useful reliable alternative method and other plant sources must be used to provide a steady supply of vital substances like camptothecin. According to the reports, the fungus *Entrophospora infrequens* from the plant *Nothapodytes nimmoniana* acts as the major source of camptothecin production. A yield attenuation was observed in endophyte *Trichoderma atroviride* containing camptothecin (Nadeem et al., 2012). Camptothecin production scaling up using endophytes was the main challenge that existed in yield amplification (Clarance et al., 2019). Three fungal species *Phomopsis sp., Alternaria alternata* and *Fomitopsis sp.,* also act as the prominent CPT producers (Shweta et al., 2013). From the chloroform extract, endophytic fungi *Entrophospora infrequens* isolated from *Nothapodytes foetida*'s inner bark tissue produce camptothecin with an absorption rate of 18 g/mg of dry weight mycelia. Camptothecin was isolated from *Entrophospora infrequens* and demonstrated cytotoxic activity against human lung cancer cells (A549), ovarian cancer cells (OVCAR-5) and liver cancer cells (HEp2) (Puri et al., 2005). Additionally, the western ghat's *Apodytes dimidiate* has been shown to have camptothecin-producing Endophytic fungus *F. solani* (Shweta et al., 2010).

The insufficient water solubility and excessive toxicity of camptothecin make it difficult to use it as an anticancer agent. To overcome these side effects 9-methoxy camptothecin (MCPT) and 10-hydroxy camptothecin (HCPT) two derivatives of camptothecin were used without the aforementioned restrictions and with the same medical effectiveness (Kusar et al., 2009). From woody climber *Pyrenacantha volubilis* four strains of bacillus bacterial endophytes were isolated. One *Bacillus subtilis* strain, KY741853, out of the four under investigation, provided the highest CPT production (0.106 mg/g), and during subculturing (up to the fifth subculture generation), CPT yield drastically reduced, going from 0.18 mg/g to 0.03 mg/g. (Soujanya et al., 2017). Several camptothecin derivatives have been identified as good anticancer agents for example IDEC-132 (9-amino camptothecin), rubitecan (9-nitro camptothecin) and 10,11-methylenedioxy camptothecin (Ulukan and Swaan, 2002). By the enzyme strictosidine synthase, action strictosidine is produced and results in the formation of secologanin (Fig: 6) and tryptamine (Fig: 5) and their compressed product is the CPT. In recent years in a few research, it was shown that certain plants, including *Ophiorrhiza pumila* (Rubiaceae), *Camptotheca acuminata* (Nyssaceae), and *Nothapodytes nimmoniana* (Icacinaceae), include candidate genes for CPT synthesis and critical enzymes for its control (Manjunatha et al., 2016; Rather et al., 2017).

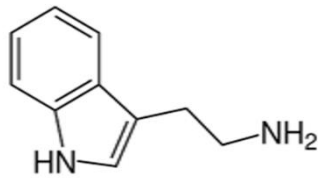


Figure 5: Tryptamine

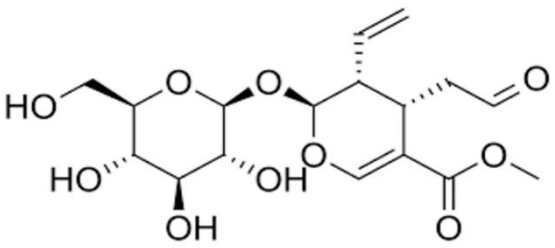


Figure 6: Secologanin

Ninety-four endophytic fungi from *Camptotheca accuminata* were recovered, and 16 of those strains were cytotoxic to Vero or PC3 cells. Camptothecin was discovered to be produced using EI-MS, TLC and HPLC analysis, and the endophytic fungus *Fusarium solani* displayed maximal cytotoxic effect against the cancer cell (Ran et al., 2017). Using high-performance liquid chromatography, it was detected that *Aspergillus niger* also produces camptothecin and it was separated from the *Piper betel*. Additionally, cytotoxic activity was found in the colon cancer cell line (Aswini and Soundhari 2018). When all of the important fungal culture parameters were optimized, the highest yield of CPT (146 mg/l) with mixed fungal (FI + F2) cultures was discovered. Experimentally, these results were contrasted with those obtained from monocultures of *Colletotrichum fructicola* F1 (33 mg/l) and *Corynespora cassiicola*-F2 (69 mg/l). *Nothapodytes nimmoniana* monocultures of *Fusarium oxysporum* isolated from the same plant produced high amounts of CPT (90 mg/l) on their own (Bhalkar et al., 2016). Endophytic fungi isolated from the bark of *Camptotheca acuminata* found to produce camptothecin were detected again (Kusari et al., 2009). Three fungi that produce camptothecin have been isolated from *C. acuminata*: *Aspergillus sp*. LY341, *Aspergillus sp*. LY355, and *Trichoderma atroviride* LY357; their respective yields were 7.93, 42.92, and 197.82 g/L. With repetitive subculture unfortunately strains LY341 and LY355 lost the camptothecin-producing capability. But from the second to eighth generation unswerving camptothecin production was observed in LY357 strain (Kai et al., 2015). Three fungal strains *Phomopsis vaccinii* (XSCY02),*Fusarium nematophilum* (XSXY09) and *Alternaria alternate* (XSQZ04) were obtained from Camptotheca acuminata were tested in submerged culture condition for CPT production (Su et al., 2014). 24 mg/g, 29 mg/g and 37 mg/g CPT were produced by these given fungal strains viz. XSCY02, XSQZ04 and XSXY09 respectively (Soujanya et al., 2017). 0.175 mg/l CPT was produced by the *Aspergillus niger* fungal strain isolated from *Piper betel* (Aswini and Soundhari 2018). According to a new study among 94 strains isolated from *Camptotheca acuminata* only one fungus, *Fusarium solani* (S-019), which is often found in the genera *M* sp., *Pestalotiopsi sp*., *Alternaria sp*., and *Cephalosporium sp*., produced CPT after 96 hours of incubation (40 5 mg/g) (Ran et al., 2017).

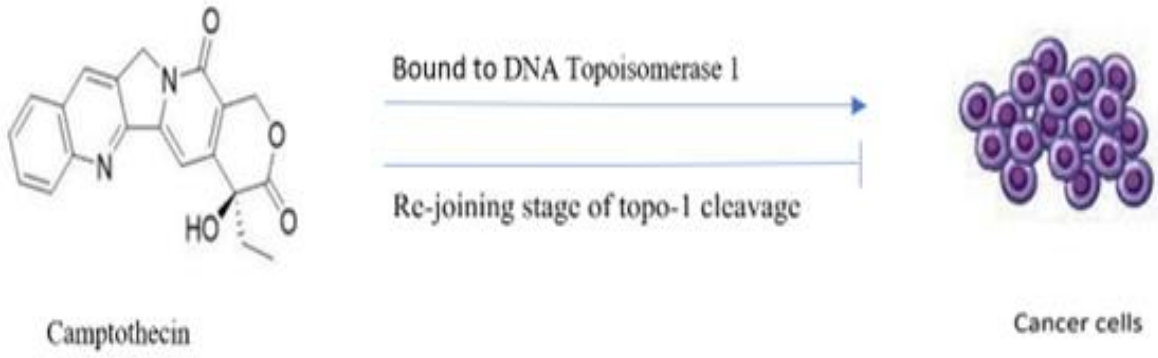


Figure: 7

D. Vinca alkaloids

Leaves of vinca plants are the natural source of bioactive compounds. Vinca plant leaves have been used for centuries to cure a variety of illnesses. Academics have stated that it also has hypoglycemic, hypotensive and purgative properties. However, these plants develop extremely slowly, and it will take a lot of leaves for extraction. In the 1950s two research teams discovered the antitumor properties of the plant. The two natural vinca alkaloids, vinblastine and vincristine, are derived from Catharanthus roseus or Vinca rosea and are used to treat lymphoma and leukaemia respectively. (Barnett et al., 1978). Vinca alkaloid isolation story was known during the late 1950s, and it was initially isolated from periwinkle in Madagascar (*Vinca rosea* is the colloquial name for the scientific name *Catharanthus roseus*). According to Jamaican folklore, in the absence of insulin, periwinkle extracts were employed as an oral hypoglycemic agent (Noble, 1990). *C. roseus* leaf extracts were identified as the treatment for diabetes, which significantly impacted 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. The cell interaction with vinca alkaloids generates the p53 tumour protein and the 1a (p21) CDK (cyclin dependent kinase), which affect the activity of protein 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 related to enhanced p53 and p21 activity, 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, *Penicillium concavoradulozum* VE89L and *Aspergillus amstelodami* VR177L, two endophytic fungi isolated from vinca plants, are able to produce vinblastine when exposed to modification by epigenetic (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).

When the cell cycle is in the metaphase, vinblastine and vincristine act as inhibitors, by attaching to the microtubules, they prevent the mitotic spindle from progressing (Kumar 2016). By the principle action of vincristine, mitotic spindle dynamics and microtubule organization are hampered, intracellular transport is disrupted, and tumour blood flow is decreased—the latter presumably as a result of anti-angiogenesis—in addition to other factors. (Zhao et al., 2010). Vinca alkaloids are the second-most often utilized family of anticancer medications in the treatment of different cancers. The coupling of catharanthine monomer and vindoline resulted in the formation of terpenoid indoles vinca alkaloids, and due to their capacity to lower the number of white blood cells in nephroblastoma and acute lymphoblastic leukaemia, they are utilized in chemotherapy. (Moudi et al., 2013). Over the course of a decade, the extract was thoroughly studied phytochemically, and many anticancer alkaloids, including vinblastine, vincristine, vinleunosine, and vinrosidine, were found. (Johnson et al., 1963; Noble 1990; Noble 2016). The first report about the case of vinblastine making by endophytic fungi is the *Alternaria* sp. secluded from the phloem of *Catharanthus roseus* vinblastine (Haiyan and Lingqi 1998). For the first time, endophytic fungi have generated high-yield vinblastine (182 g/L). It was originally noted that *Curvularia verrucalosa* was more prevalent than other fungus (Parthasarathy et al., 2020)

Alternaria sp. of endophytic fungi produce vinblastine (Guo and Zhang 1998) and one or more species of *Fusarium oxysporum* can generate 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%). Fungal endophytes were explored as an alternate approach to prevent plant extinction and to lower the price of these medications (Kumar 2016). Vinblastine and vincristine are two prescription medications used to treat Hodgkin lymphoma. In phase-II/III studies for the treatment of breast cancer and carcinoma, vinca alkaloids along with structural analogues (such as vinflunine, vinorelbine, and anhydrovinblastine) that target tubulin polymerization are used (Kaur et al., 2014). Vinblastine was discovered in the fungal endophyte *Nigrospora sphaerica*, which was later tested against breast cancer cell lines. It was obtained from Catharanthus roseus. MDA-MB 231 (Ayob et al., 2017). The yield of dimeric alkaloids was very poor. Since it is challenging to develop shoots in a bioreactor, growing *Catharanthus roseus* in the field proved significantly more cost-effective (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 by using the same instinct to make time for duties related to nature conservation and using various fungal endophytes from *Catharanthus roseus* as the source (Kumar et al., 2013). Vincristine and vinblastine concentrations in *Talaromyces radicus, endophytic* fungi from *C. roseus* were 670 g/L and 70 g/L, respectively. HeLa, MCF7, A549, U251, and A431 cells were used to examine the cytotoxicity of vincristine that had been partially purified. Vincristine was found to have a dose-dependent effect on growth inhibition in the HeLa, MCF7, A549, U251 and A431 cell lines with IC50 values of 4.2, 4.5, 5.5, 5.5, and 5.8 g/mL, respectively. However, significant impacts were not observed on normal cells HEK293 (Palem et al., 2016; Song et al., 2016).

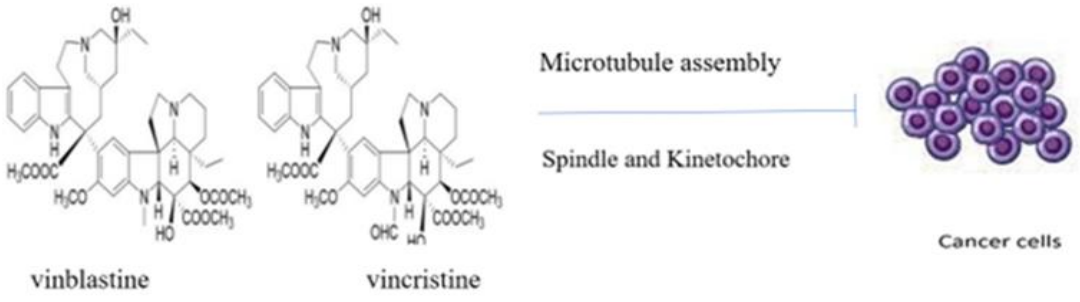


Figure: 8

E. Piperine

Piperine is found in the fruits of pepper plants *Piper longum* L. (long pepper) and *Piper nigrum* L (black pepper*)* which is accountable for the pungent taste of those fruits. It has anti-inflammatory and anticancer properties. It is a potent anticancer alkaloid (Zheng et al., 2016). Angiogenesis, cell cycle inhibition, activation of apoptotic signalling cascades, control of autophagy, and reduction of cell proliferation are examples of chemo-preventive mechanisms of piperine. Piperine has antidiabetic properties in which it enhances the increased hepatic glutathione oxidation while lowering renal glutathione levels and renal glutathione reductase activity (Manayi et al., 2019). Piperine also inhibits the expression of interferon regulatory factors caused by lipopolysaccharide, decreases the liver marker enzyme activity, decreases STAT1 activation and blocks the production of Th-2-mediated cytokines, both of which indicate an anti-inflammatory effect. Piperine's anticancer activity is manifested in the following ways: activation of caspase-3 and caspase-9, cleavage of poly (ADP ribose) polymerase (PARP), upregulation of Bax protein and downregulation of Bcl-2 protein, downregulation of phosphorylated STAT3 and NF- transcription factors, inhibition of extracellular signal-regulated kinase (ERK1/2), AKT signalling pathways and p38 MAPK and inhibits matrix metalloproteinase (MMP)-9 expression signal matrix metalloproteinase (MMP)-9 expression stimulated by epidermal growth factor (EGF)-induced (Stojanovi et al., 2019).

The anti-cancer and anti-invasive properties of piperine have been explained by suppressing the production of MMP-9 and MMP-13, which also reduce NF- and AP-1 activation and PKC and ERK phosphorylation, respectively (Hwang et al., 2011). According to recent research, piperine inhibits angiogenesis in human umbilical vein endothelial cells (HUVECs) via phosphoinositide-3 kinase (PI3K)/Akt signalling (Doucette et al., 2013: Karar and Maity 2011). It has the capacity to increase the bioavailability of specific medications and minerals. The cultures of endophytic fungal species such as *Mycosphaerella* sp. C. *gloeosporioides*, and *Periconia* sp. isolated from *Piper* sp. 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). In addition to inhibiting mTORC1 activity in Caco-2 and HT-29 cells, piperine also demonstrates suppression of prostate cancer cells (LNCaP and PC3) through the induction of autophagy (Yun et al., 2013). In TRIAL (tumour necrosis factor-related apoptosis-inducing ligand) based therapy piperine is utilized as an adjuvant that inhibits the phosphorylation of survivin and p65 to cause apoptosis in TRAIL-sensitive and TRAIL-resistant triple-negative breast cancer (TNBC) cells. (Abdelhamed et al., 2014; Merino et al., 2007). By altering the self-renewal capabilities of cancer stem cells and reducing the Wnt/b-catenin signaling pathway (CSCs) piperine inhibits the CSCs (Kim et al., 2012; Li et al 2011).

F. Pyrans and Pyrones

Pyran is one of the most important non-aromatic structures found in nature. Which contains a six-membered ring with five carbon atoms and one oxygen in it. Pyran and its derivatives show a wide range of bioactivities, most importantly they show anti-cancer properties (Grover et al., 2022). Two novel pyrans 5-butyl-6-(hydroxymethyl)-4- methoxy-2H-pyran-2-one and 4-methoxy-6-methyl-5- (3- oxobutyl) -2H-pyran-2-one are obtained from *Alternaria phragmospora*, an endophytic fungus from *Vinca rosea* leaves which showed modest antileukemic activity 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. isolated from the stem of *Aquilaria sinensis* shows the occurrence of a new benzopyran, (2R*, 4R*)-3,4-dihydro 4-methoxy-2- methyl-2H-1-benzopyran-5-ol. Compared to cisplatin (positive control), it exhibits comparatively low cytotoxicity against the cell line SF-268 at a dosage of 100 mg/ml (Wu et al., 2010)

The α-Pyrones are one of the most important structural features found in a huge variety of biologically active metabolites. Through in vitro scrutiny of cytotoxic inhibition upon the application of naphtha-gamma pyrone, TMC 256 A1, Cancer cells SNB19, MCF-7, Hep3B, MDA-MB-435, Huh7, and U87 MG were inhibited cytotoxically (IC50 19.92–47.98 M). 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 serves as the primary source of pyrone metabolites and its derivatives (Liu et al., 2011). Nigerapyrone B is the derivative of α-Pyrone derivative of -pyrone discovered in the inner tissues of the maritime mangrove plant *Avicennia marina* by the endophytic fungus *Aspergillus niger* MA132. Nigerapyrone B demonstrated selective efficacy against the HepG2 cell line with an IC50 of 62 μM. The tumour cell lines A549, HepG2, DU145, MCF-7, SW1990, NCI-H460, and MDA-MB-231 were all affected by the cytotoxic activity of positive control fluorouracil, with IC50 values of 52, 109, 3.3, 31, 121, 8.5, and 59 μM, respectively (Huang et al., 2011).

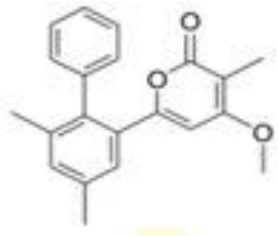
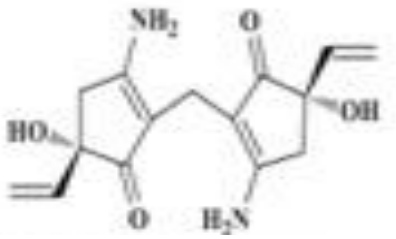
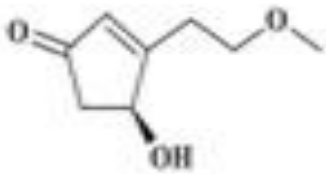


Figure 9: Nigerapyrones B

G. Alkaloids

Alkaloids are nitrogen-containing compounds with low molecular weight, pharmaceutically very significant due to their high biological activities. They are generally made from amines, which are created by amino acids like histidine, lysine, ornithine, tryptophan, and tyrosines are decarboxylated. 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 generated from plants that have a wide range of bioactivities, including toxicity, therapeutic benefits, and recreational uses, several of them have also been isolated from fungal endophytes. Alkaloids are obtained from plants for their use as potential agents against cancer and many of them are obtained from fungal endophytes (Kharwar et al., 2011). Diverse biological activities like anti-viral, anti-fungal and anti-cancer properties are carried out by secondary metabolites alkaloids as they are produced by endophytic fungi (Silva et al., 2007). With IC50 values between 0.05-0.75 ppm, the endophytic fungus *Hypomontagnella monticulos* Zg15SU isolated from *Zingiber grifthii* produced griffithiiene, a novel terpenoid-alkaloid skeleton-based compound with strong potential against pancreatic, bladder, and colon cancer cell lines (HCT116, Panc-1 and NBT-T2,) (Lutfa et al., 2021). Ascomylactams A–C are three new alkaloids extracted from the fungal endophyte *Didymella* sp. of mangrove plant. 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 seperated from *Hippeastrum calyptratum* Herb. and *Hippeastrum aulicum* Herb. (Andrade et al., 2014). The biological properties of alkaloids generated from plants have a wide range of bioactivities, including toxicity, therapeutic benefits, and recreational uses, Studies have been conducted on various alkaloids extracted from plants, mainly from endophytic fungi as well used as possible medicines fighting against cancer (Kharwar et al., 2011). A neoteric alkaloid composite GKK1032C, separated from the mangrove plant-related endophytic fungus *Penicillium* sp. CPCC 400817. 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*, has anti-inflammatory effects against IL-1 β and TNF-α and cytotoxic action against U967 and HL60 cell lines evi(Zhou et al., 2017).





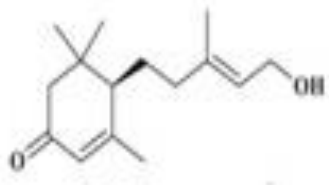


Figure 10: Atrichodermone A **Figure 11: Atrichodermone B** **Figure 12: Atrichodermone C**

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

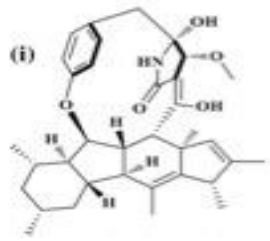


Figure 13: Ascomylactam

Chaetomugilide, a unique alkaloid discovered in the *Chaetomium globosum* TY1 fungus inhabiting the outermost layers of stems of *Ginko biloba* shows antineoplastic activity towards human hepatoblastoma HepG2 (Yuan et al., 2019). Against HepG2 chaetomugilide A shows a substantial degree of cytotoxicity (IC50 1.7 µM), Chaetomugilides B and C and chaetoviridin E were applied to the same HepG2 cell line, and both showed significant cytotoxicity (IC50 1.7 M) and moderate cytotoxicity (IC50 19.8-53.4 M) levels (Li et al., 2013). Endophytic fungi *Aspergillus fumigatus* associated with plant *Cynodon dactylon* produces 9-Deacetyl Fumigar Lavine C11, shown cytotoxicity towards human leukaemia cells (K562), a drug currently used in leukaemia with IC50 3.1 µM comparable to the leukaemia medication doxorubicin hydrochloride (1.2 µM) (Liu et al., 2004). An alkaloid compound called variecolorin grand alkaloid E-7 and an alkaloid called dioxopiperazine alkaloid were both present in a fungal endophyte *Eurotium rubrum that* was isolated from tissues of the plant *Hibiscus tiliaceus* (Wang et al., 2007). From the *Desmotes incomparabilis leaf* tissues isolated an endophytic fungus under *Mycoleptodiscus* sp. produces Mycoleptodiscus B, which has anticancer activity against the prostate, lung, and skin cancer cell lines A2508, IMR-90, PC-3, H460 and H522-T1, with IC50 values of 0.780, 0.4, 1 0.600, 0.660 and 0.630 µM (Ortega et al., 2013).

H. Lactones

Lactones are formed by ω oxidation, lactonization (cyclization) of the hydroxyl acids, and β oxidation, these are certain pathways through which lactones are made. They are polyketide-derived cyclic esters (Krzyczkowska et al., 2017). *Chaetomium chiversii* and *Ephedra fasciculate* were used to isolate radicicol, a prevailing lactone called radicicol and it is a prominent agent inhibiting the propagation of the cell line MCF-7 (Turbyville et al., 2006). Medicinal herb *Ajuga decumbens,* inhabiting *Myrothecium roridum* produces myrotheciumone a bicyclic lactone, and exhibits cytotoxicity against A549, HepG2, MCF-7, HL-7702, SMMc-7721, and QSG-7701 cell lines (Lin et al., 2014). Photipyrone B is a compound acquired from the endophytic fungi *Pestalotiopsis photiniae* isolated from the plant *Roystonea Regia.* China. It has a repressing effect on MDA-MB-231 (Ding et al., 2012). Another complex called Brefeldin A exhibits antiviral, anticancer and antifungal activities and it was secluded from various fungi, for example, Cercospora, *Aspergillus clavatus* Ascochyta, Alternaria Curvularia, *Paecilomyces* sp. Penicillium and Phyllosticta (Wang et al., 2002).

I. Terpenoids

They are amended 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, terpenes are numerous naturally occurring substances that have enormous medicinal potential. Biosynthesized through the mevalonate pathway using enzyme terpene cyclase enzymes. Approximately 50,000 terpenoid metabolites are there which include sesquiterpenes, di-terpenes, and monoterpenes representing around 400 discrete structural families that were isolated from fungi, bacteria and plants. 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.* These two substances exhibit negligible cytotoxic action in IN vitro tests against six human tumour cell lines (A2780, Bel-7402, HCT-8, BGC-823, MCF7, and A549) thru IC50>10−5 M (Ge et al., 2011). Relatively all these widely occurring metabolites are present in prokaryotes in a minor fraction (Yamada et al., 2015). Increased oxygenous sesquiterpenoid content in *A. lancea* (a medicinal plant in China, that contains oxygenous sesquiterpenoids) was observed due to the generation of reactive oxygen species (ROS) 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 dynamic antimalarial value (Woodrow et al., 2005). There is evidence for the existence of a great number of additional biological uses for artemisinin, such as anti-inflammatory, immunoregulatory, and anticancer properties, all without the danger

of the emergence of drug resistance. (Das 2015). Phomoarcherins A-Ce three novel sesquiterpenes obtained from the *Phomopsis archeri* endophyte residing inside the stem of *Vanilla albidia.* Among these compounds, With IC50 values of 8.0, 0.1, 2.0, 20, 5.0, and 9.4 g/mL, respectively, phomoarcherin B demonstrated in vitro cytotoxic activity against the KKU-100, KKU-M139, KKU-M156, KKU-M213, KKUM214, and KB cell lines. With IC50 values of 8.9, 8.9, 18.0, 15.4, and 18.8 g/mL, respectively, phomoarcherin C demonstrated in vitro cytotoxic activity against the KKU-100, KKU-M139, KKU-M156, KKU-M213 and KKU-M214 cell lines. With IC50 values of 16.6, Phomoarcherin A demonstrated in vitro cytotoxic activity against KKU-M213 cell lines (Hemtasin et al., 2011). Fungal endophyte *Paraconiothyrium* sp. MY-42 was used in the isolation of isopimarane diterpenes, which exhibit moderate cytotoxic activity against human leukaemia cells, promyelocytic HL60 (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). Triterpenoid toosendanin is the primary bioactive constituent present in fruits and bark of traditional anthelmintic and insecticidal plants *Melia azedarach* and *Melia toosendan* (TSN) (Wang et al., 2007). TSN acts as a potential antitumor drug against various tumours and involves estrogen receptor (ER) and p53 protein upregulation, activation of the mitochondrial apoptotic pathway, and suppression of STAT3, a new target for cancer therapy (Gao et al., 2019)

Sesquiterpenes, ceriponol F, ceriponol G and ceriponol K were extracted from the fungus *Ceriporia lacerate* inhabiting a medicinal plant *Huperzia serrata* (Chen et al., 2016). The cytotoxic activity of cerpinol F and cerpinol K against HeLa, HepG2, and SGC 7901 is modest (IC50: 32.3 0.4-173.2 1.5 M). As opposed to ceriponol G, which exhibits marginally enhanced cytotoxicity toward HeLa cells (Ying et al., 2013).

Cercosporene F is a new guanacastane diterpene obtained from an endophytic fungus *Cercospora* sp. secluded from the leaves of *Fallopia japonica*. Fungus *Cercosporene* F exhibits cytotoxic effects on 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 sequestered from the roots of Indian Coleus (*Coleus forskohlii*) which is characterized by antineoplastic, anti-HIV activities. Further endorsed forskolin uses range from lipolysis and body weight management to hypertension and heart failure (Pateraki et al., 2017). Compound Perenniporin A was isolated from *Perenniporia tephropora* Z41 a fungal endophyte inhabiting *Taxus chinensis* var. mairei bark, and showed simply a moderate amount of cytotoxicity towards cell lines HeLa, SMMC-7721, and PANC-1 with IC50 values 30.44, 45.49, 44.22 μg/mL correspondingly (Wu et al., 2013).

From a fungal endophyte penicillium, one azaphilone and two meroterpenes were isolated from seawater. Given three complexes exhibit cytotoxicity against MDA-MB-435, HepG2, HCT116 and the IC50 values for the A549 cell lines are 34.25, 24.56, 33.72, 37.82 μM (Li et al., 2014).

J. Quinones

Quinones are commonly found among kingdom plants, primarily in higher plants from the families such as Polygonaceae, Labiatae, Rubiaceae, Leguminosae, Boraginaceae, Rhamnaceae (Tyagi et al., 2021). Usually, they can be found in a variety of living organisms like humans, bacteria and plants and fungi were the source of their conjugated structure. *Eurotium rubrum,* endophytic fungi isolated from the inner tissue's mangrove plant *Hibiscus tiliaceous* produces a compound called 9-dehydroxyeurotinone has an anticancer activity against SW1990 cell lines with IC50 about 25 μg/mL (Chen et al., 2016). 2,3-didehydro-19α-hydroxy14-epicochlioquinone B, the novel cytotoxic compound isolated from the species *Nigrospora*, MA75 residing in the stem of *Pongamia pinnata* the marine mangrove plant. 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 instance, the shikimate pathway uses precursors generated from chorismite to create isoprenoid quinones, while NRPS creates terrequinone from L-tryptophan, tyrosinase creates dopaquinone from tyrosine, and catechol oxidase/PKS creates benzoquinone from catechol. (Feng et al., 2015). Compounds like benzene or naphthalene are aromatic compounds, in which quinones act as their derivative. Alterporriol (Fig: 14**)** an Anthanoid compound extracted from rice culture of *Stemphylium globuliferum* an endophytic connected with the medicinal plant *Mentha pulegium* has an EC50 value of 2.7 g/mL and is cytotoxic to the L5178Y cancer cell line (Debbab et al., 2010)

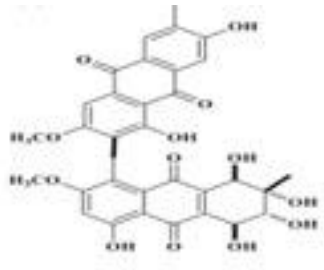


Figure 14: Alterporriol

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

Table 1. Novel cytotoxic substances discovered in endophytes

Compounds	Chemical nature	Cell line	Fungus	Host	References
Myrotheciumone A	Lactones	HepG2, A549, HL-770QSG-7701, MCF-7,	*Myrothecium roridum*	*Ajuga decumbens*	Lin et al., 2014
(+) - (4R,8R) - foedanolide	Lactones	U-251, HeLa, HepG2, MCF-7 A-549,	*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* species (Strain- ZW02)	*Ilex canariensi*	Lu et al., 2011
Asperlactone G Asperlactone H	Lactones	A-549 A-549	*Aspergillus* species	*Pinellia ternate*	Xin et al., 2019

Compounds	Chemical nature	Cell line	Fungus	Host	References
Brefeldin A 37	Lactone	HL - 60, HeLa Spc-A-1 1.0, KB MCF-7	*Paecilomyces* species and *Aspergillus clavatus*	*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 L et al., 2006
Epicocconigrone A	Polyketides	RAJI	*Epicoccum nigrum*	*Mentha suaveolens*	Amrani et al., 2013
AcremoxanthoneE	Polyketides	SKLU-1PC-3, K562, U251, HCT-15, MCF-7,	*Acremonium camptosporum*	*Bursera simaruba*	Melendez-Gonzalez et al., 2015
Preussilide E	Unclassified Polyketide	SKOV-+3 KB3.1, A431, L929, A-549	*Preussia similis*	*Globularia alypum*	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, A431 SKOV3, KB3.1, A549	*Preussia similis*	*Globularia alypum*	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	A431, L929 KB3.1, PC3, A549 SKOV3	*Preussia similis*	*Globularia alypum*	Noumeur et al., 2017
Isocochlioquinone D	Meroterpenoids	MCF7, SF268 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, SMMC7721 HCT116 CaCo2 A-549	*Penicillium* sp.sh18	*Isodon eriocalyx* (T)	Tang et al., 2019
Isopenicin B		SW480 SW620, HCT116 CaCo2			

Compounds	Chemical nature	Cell line	Fungus	Host	References
Talaperoxide B Talaperoxide D	Peroxides	HeLa, MDA-MB-435, MCF-7PC-3 HepG2, HepG2, MCF-7, PC-3 MDA-MB-435, HeLa,	*Talaromyces flavus*	*Sonneratia apetala*	Li et al., 2011
Cladosporone A	Others	Hela, K562, BGC823, A549, HL-60, U937, MOLT-4, Huh-7, MCF-7, H1975,	*Cladosporium* sp.	*Kandelia candel*	Ai et al., 2015
Dihydronaphthalenone 5-hydroxy dihydrofusarubin B 5-hydroxyl dihydro fusarubin A	Phenolic compounds	Vero, MCF-7, KB, NCI-H187, NCI-H187,KB, Vero, MCF-7, MCF-7, KB, 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, SW1990, HepG2, NCIH460, MCF-7, SGC-7901, SW480, U251	*penicillium brocae* MA231	*Avicennia marina*	Meng et al., 2014
Penicibrocazine B		MCF-7, Du145, SW480, HepG2, U251 SGC-7901, HeLa, NCIH460, SW1990,			
Penicibrocazine E		SGC-7901, U251 Du145, SW1990, MCF-7, HeLa, NCIH460, SW480, HepG2,			
Penicibrocazine F		SW1990, U251 HeLa, NCIH460, HepG2, GC-7901, SW480, Du145, MCF-7,			
Merulin A	Terpene	BT474, SW620	Basidiomycete-XG8D	*Xylocarpus granatum*	Chokpaiboon et al., 2010
Merulin C		BT474, SW620			

CONCLUSION

This review discussed the significance of fungal endophytes, as a source of secondary metabolites and various bioactive molecules which are used as a natural weapon against deadly diseases. Years back endophytes attracted the interest of the scientific community, because of their potential use in the pharmaceutical industry. Endophytes, the group of microorganisms residing inside of the robust plant tissue in harmony with the plant environment, exhibit complex interaction with their host for coexistence. During this time period, endophytes have the potential to acquire a variety of noteworthy traits. In order to keep symbiosis steady, a wide variety of enzymes are involved in the process of colonization and growth. In biological conversion, endophytes are more beneficial and selective due to their unique habitat and they produce biologically active novel metabolites. The fungal metabolites under consideration have a widespread cytotoxic effect, depending on the tumour cell lines and the cytotoxicity may vary depending on cell lines.

Genetic engineering in the future will enable researchers to isolate and uncover novel ways and fungal strains that produce anticancer chemicals. Assessing the new metabolic pathways for mass metabolite production 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 J L, del Olmo E, García-Fernández L F, Francesch A, Trigili C, Barasoain I, Andreu J M, Díaz J F, 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. Epub 2014 Sep 24. PMID: 25248726.
6. Amna T, Puri S C, Verma V, Sharma J P, Khajuria R K, Musarrat J, Spiteller M, Qazi G N. (2006). “Bioreactor studies on the endophytic fungus *Entrophospora infrequens* for the production of an anticancer alkaloid camptothecin,” Can J MicrobiolMar;52(3):189-96PMID: 16604115.
7. Amrani E l M, Lai D, Debbab A, Aly A H, 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):49-56PMID: 24328302.
8. Andrade J P de, Guo Y, Font-Bardia M, Calvet T, Dutilh J, Viladomat F, Codina C, Nair J J, Zuanazzi JAS, Bastida J. (2014). “Crinine-type alkaloids from *Hippeastrum aulicum* and *H. calyptratum*. Phytochemistry,” j. phytochem.2014.03.007. Epub. PMID: 24768284.
9. 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.
10. 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,
11. 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.
12. Ayob F W, 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. Epub 2017 Jun 14. PMID: 28612376; PMCID: PMC5481544.
13. Backman P A, and Sikora R A, (2008). “Endophytes: An emerging tool for biological control, Biological Control,” Volume 46, Issue 1, Pages 1-3, ISSN 1049-9644. j.biocontrol. 03.009.
14. Bacon C W, White J F. (2016). “Functions, mechanisms and regulation of endophytic and epiphytic microbial communities of plants,” Symbiosis 68, 87–98.
15. Balunas M J, Kinghorn A D. (2005). “Drug discovery from medicinal plants,” Life Sci. 2005 Dec 22;78(5):431-41. j.lfs.2005.09.012. Epub. PMID: 16198377.
16. 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 Therapeutic,”. Curr Microbiol 78, 1699–1717
17. Barnett C J, Cullinan G J, Gerzon K, Hoying R C, Jones W E, Newlon W M, Poore G A, Robison R L, Sweeney M J, Todd G C, Dyke R W, Nelson R L. (1978). “Structure-activity relationships of dimeric Catharanthus alkaloids. 1. Deacetylvinblastine amide (vindesine) sulfate, J Med Chem. Jan;21(1):88-96.
18. Bedi A, Adholeya A, Deshmukh S K. (2017). “Novel anticancer compounds from endophytic fungi,” Volume 6, No. 1 Current Biotechnology. 7:168–18.
19. Bedi P, Gupta R Pramanik T. (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.
20. Bertrand S, Bohni N, Schnee S, Schumpp O, Gindro K, Wolfender J L. (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.

21. Bhalkar B N, Patil S M, Govindwar S P. (2016). “Camptothecine production by mixed fermentation of two endophytic fungi from *Nothapodytes nimmoniana*,” Fungal Biol. Jun-Jul;120(6-7):873-83. Epub. PMID: 27268247.
22. 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
23. Bjornsti M. A, Benedetti P, Viglianti G. A. and J. C. Wang. (1989). “Cancer Res, 49, 6318.
24. Blagosklonny M V. (2004). “Analysis of FDA approved anticancer drugs reveals the future of cancer therapy. Cell Cycle,”;3(8):1035-42. Epub 2004 Aug 16. PMID: 15254418.
25. Bo G, Haiyan L, Lingqi Z. (1998). “Isolation of a fungus producting vinbrastine,” J Yunnan Univ 20(3):214–215
26. Brito D A, Yang Z, Rieder C L. (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. PMID: 18710927; PMCID: PMC2518701.
27. Cao P, Yang J, Miao C P, Yan Y, Ma Y T, Li X N, Zhao L X, Huang S X. (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.
28. 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.
29. Chandra S. (20120). “Endophytic fungi: novel sources of anticancer lead molecules,” Appl Microbiol Biotechnol. Jul;95(1):47-59. Epub 2012 May 24. PMID: 22622838.Chandra, S. (2012). Endophytic fungi: novel sources of anticancer lead molecules. Appl. Microbiol. Biotechnol. 95, 47–59.
30. Chen J Y, Tang Y A, Li W S, Chiou Y C, Shieh J M, Wang Y C. (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.
31. 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.
32. Chen L, Zhang Q Y, Jia M, Ming Q L, 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.
33. 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.
34. Chithra S, Jasim B, Anisha C, Mathew J, Radhakrishnan E K. (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. Epub 2014 Apr 2. PMID: 24691878.
35. Chithra S, Jasim B, Sachidanandan P, Jyothis M, Radhakrishnan E K. (2017). “Piperine production by endophytic fungus *Colletotrichum gloeosporioides* isolated from *Piper nigrum*. Phytomedicine,” Mar 15;21(4):534-40. phymed.2013.10.020. Epub 2013 Nov 21. PMID: 24268806.
36. 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. j. Nat. Prod., 2010, 73, 1005–1007
37. 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*.
38. Clark R, Lee S H. (2016). “Anticancer Properties of Capsaicin Against Human Cancer,” Anticancer Res.;36(3):837-43. PMID: 26976969.
39. Cortés F, Pastor N. (2003). “Induction of endoreduplication by topoisomerase II catalytic inhibitors. Mutagenesis,” Mar;18(2):105-12. PMID: 12621064.
40. Cragg G M, Boyd M R, Cardellina II J H, Grever M R, Schepartz S, Snader K M, 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.
41. Dancey J, Eisenhauer E A. (1996). “Current perspectives on camptothecins in cancer treatment,” Br J Cancer. Aug;74(3):327-38. PMID: 8695345; PMCID: PMC2074644.
42. Das A K. (2015). “Anticancer Effect of AntiMalarial Artemisinin Compounds,” Ann Med Health Sci Res. Mar-Apr;5(2):93-102. PMID: 25861527; PMCID: PMC4389338.
43. Debbab A, Amal H. Aly, Wen H. Lin, Proksch P. (2010). “Bioactive Compounds from Marine Bacteria and Fungi,” Volume3, Issue5, Special Issue: Marine Omics.
44. Demain A L, Vaishnav P. (2011). “Natural products for cancer chemotherapy. Microb Biotechnol.” Nov;4(6):687-99. Epub 2010 Nov 18. PMID: 21375717; PMCID: PMC3815406.
45. Devari S, Jaglan S, Kumar M, Deshidi R, Guru S, Bhushan S, Kushwaha M, Gupta A P, Gandhi S G, Sharma J P, Taneja S C, Vishwakarma R A, Shah B A. (2014). “Capsaicin production by *Alternaria alternata*, an endophytic fungus from *Capsicum annum*; LC-ESI-MS/MS analysis,” Phytochemistry. Feb; 98:183-9. j. phytochem.2013.12.001. Epub 2013 Dec 28. PMID: 24378219.
46. Dhayanithy G, Subban K, Chelliah J. (2019). “Diversity and biological activities of endophytic fungi associated with *Catharanthus roseus*,” BMC Microbiol;19(1):22. PMID: 30665368; PMCID: PMC6341747.
47. Ding G, Qi Y, Liu S, Guo L, Chen X. (2012). “Photipyrones A and B, new pyrone derivatives from the plant endophytic fungus *Pestalotiopsis photinia*e,” J Antibiot (Tokyo). 65(5):271-3. Epub 2012 Mar 14. PMID: 22415458.
48. Doucette C D, Hilchie A L, Liwski R, Hoskin D W. (2013). “Piperine, a dietary phytochemical, inhibits angiogenesis,” J Nutr Biochem. Jan;24(1):231-9. Epub. PMID: 22902327; PMCID: PMC3524266.
49. Drukman S, Kavallaris M. (2002). “Microtubule alterations and resistance to tubulin-binding agents (review),” Int J Oncol;21(3):621-8. PMID: 12168109.
50. 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
51. Elkhayat E Goda A. (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,
52. El-Tarabily K, Hardy S J, 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
53. 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,
54. Eyberger A L, Dondapati R, Porter J R. (2006). “Endophyte fungal isolates from *Podophyllum peltatum* produce podophyllotoxin,” J Nat Prod. 69(8):1121-4. PMID: 16933860.

55. Farias K J S, Machado P R L, de Almeida Júnior R F, Lopes da Fonseca B A. (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. PMID: 32974532; PMCID: PMC7470301.
56. Feher M, Schmidt J M. (2003). “Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry,” J Chem Inf Comput Sci 43(1):218–227.
57. 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. Epub 2015 Aug 24. PMID: 26305932; PMCID: PMC4568701.
58. 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. Epub 2014 Feb 27. PMID: 24576210.
59. 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.
60. Fiołka M J K, Grzywnowicz J, Rzymowska K, Lewtak R, Szewczyk E, Mendyk R, Keller. (2015). “Antitumour and apoptotic effects of a novel Tris-peptide complex obtained after isolation of *Raoultella ornithinolytica* extracellular metabolites,” Journal of Applied Microbiology, Volume 118, Issue 6, 1, Pages 1357–1369
61. 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;118(6):1357-69. Epub. PMID: 25809524.
62. 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,
63. 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.
64. 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;20(1):135-140 Epub May 9. PMID: 31115517; PMCID: PMC6579966.
65. Gao Y, Lu Q, Pu Zang P, Li Xue, Ji Qing, He Zhongmei, Zhao Y, He Yang, Zhao X, Zhang L. (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
66. Ge H L, Zhang D W, Li L, Xie D, Zou J H, Si Y K, Dai J. (2011). “Two new terpenoids from endophytic fungus Periconia sp.,” F-31. Chem Pharm Bull (Tokyo).;59(12):1541-4. PMID: 22130377.
67. Gordaliza M. (2007). “Natural products as leads to anticancer drugs,” Clin Transl Oncol 9(12):767–776.
68. Gouda S, Das G, Sen S K, Shin H S, Patra J K. (2016). “Endophytes: A Treasure House of Bioactive Compounds of Medicinal Importance. Front Microbiol. 29; 7:1538. PMID: 27746767; PMCID: PMC5041141.
69. Granados G M, McTaggart A R, Rodas C A, Roux J, Wingfield M J. (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.
70. Grover P, Bhardwaj M, Mehta L, Kapoor G, Chawla P A. (2022). “Current Developments in the Pyran-Based Analogues as Anticancer Agents,” Anticancer Agents Med Chem. 2022;22(19):3239-3268. PMID: 34802409.
71. Guerram M, Jiang Z Z, Zhang L Y. (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
72. 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.
73. Guo B, Li H, Zhang L. (1998). “Isolation of the fungus producing vinblastine,” J Yunnan University Nat Sci Edition. 20:2145
74. Hawksworth D L, Lücking R. (2017). “Fungal Diversity Revisited: 2.2 to 3.8 million Species,” Microbiol Spectr.;5(4). FUNK-0052-2016. PMID: 28752818.
75. 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.
76. 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, World Journal of Microbiology and Biotechnology,1461-1469
77. Huang C H, Pan J H, Chen B, Yu M, Huang H B, Zhu X, YJ L, She Z G, Lin Y C. (2011). “Three bianthraquinone derivatives from the mangrove endophytic fungus Alternaria sp. ZJ9-6B from the South China Sea,” Mar Drugs 9:832–843
78. Hwang Y P, Yun H J, Kim H G, Han E H, Choi J H, Chung Y C, Jeong H G. (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.
79. Jakubas P 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.
80. 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.
81. Ji Y, Bi J N, Yan B, Zhu X D. (2006). “Taxol-producing fungi: a new approach to industrial production of Taxol,” Chin J Biotechnol 22:1–6
82. 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.
83. Joshi R D, Kulkarni N S. (2016). “Optimization studies on L-asparaginase production from endophytic bacteria,” Int J Appl Res 2:624–629
84. 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.
85. 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.
86. Kampfer P. (2006). “The family Streptomycetaceae, part I: taxonomy. In: Dworkin M (ed) The prokaryotes,” vol. 3 Springer, Berlin, pp 538–604
87. 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.
88. Karar J, Maity A. (2011). “PI3K/AKT/mTOR pathway in angiogenesis,” Front Mol Neurosci 4:51.

89. Katoch M, Shipra P, Shagun V, Shashank S. (2017). “Diversity, Phylogeny, anticancer and antimicrobial potential of fungal endophytes associated with *Monarda citriodora* L.,” BMC Microbiology. 17.
90. 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
91. 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.
92. 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
93. 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
94. 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
95. Kharwar R N, Mishra A, Gond S K, Stierle A, Stierle D. (2011). “Anticancer compounds derived from fungal endophytes: their importance and future challenges,” Nat Prod Rep 28:1208–1228
96. Kim Y S, Farrar W, Colburn N H, Milner JA. (2012). “Cancer stem cells: potential target for bioactive food components,” J Nutr Biochem 23(7):691–698.
97. 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.
98. 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.
99. 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
100. 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
101. 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. Erratum for: Pathogens. 2021 Nov 06;10(11): PMID: 36015072; PMCID: PMC9415982.
102. Kumar A, Patil D, Rajamohanan P R, 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.
103. Kumar A. (2016). “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,
104. 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
105. 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]
106. 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.
107. Kusari S, Zühlke S, Spiteller M. (2009). “An endophytic fungus from *Camptotheca acuminata* that produces camptothecin and analogues,” J Nat Prod;72(1):2-7. PMID: 19119919.
108. Lau D H, Xue L, Young L J, Burke P A, Cheung A T. (1999). “Paclitaxel (Taxol): an inhibitor of angiogenesis in a highly vas-cularized transgenic breast cancer,” Cancer Biother Radiopharm.;14(1):31–3610
109. 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.
110. 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. Epub. PMID: 21545109.
111. Li J, Sun H, Jin L, Cao W, Zhang J, Guo C Y, Ding K, Luo C, Ye W C, Jiang R W. (2013). “Alleviation of podophyllotoxin toxicity using coexisting flavonoids from *Dysosma versipellis*.” PLoS One;8(8): e72099. journal. pone.0072099. PMID: 23991049; PMCID: PMC3749096.
112. Li J, Yang X, Lin Y, Yuan J, Lu Y, Zhu X. (2014). “Meroterpenes and azaphilones from marine mangrove endophytic fungus Penicillium,”. Fitoterapia; 97: 241-6
113. 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
114. 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.
115. Liang Z, Zhang J, Zhang X, Li J, Zhang X, Zhao C. (2016). “Endophytic fungus from *Sinopodophyllum emodi* (Wall.) yinghat produces podophyllotoxin,” J. Chromatogr. Sci. 54, 175–178.
116. 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. Epub. PMID: 24775302.
117. Lissoni P, Fugamalli E, Malugani F, Ardizzoia A, Secondino S, Tancini G, Gardani G S. (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. PMID: 11192826.
118. Liu D, Li X M, Meng L, Li C S, Gao S S, Shang Z, Proksch P, Huang C G, Wang B G. (2011a). “Nigerapyrones A–H, a-pyrone derivatives from the marine mangrove-derived endophytic fungus *Aspergillus niger* MA-132,” J Nat Prod 74:1787–1791
119. 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 s*p. A593,” Natural Product Research, 34, 2430–2436
120. Liu J Y, Song Y C, Zhang Z, Wang L, Guo Z J, Zou W X, Tan R X. (2004). “*Aspergillus fumigatus* CY018, an endophytic fungus in *Cynodon dactylon* as a versatile producer of new and bioactive metabolites,” J Biotechnol 114:279–287.
121. Liu L F, Desai S D, Li TK, Mao Y, Sun M, Sim S P. (2000). “Mechanism of action of camptothecin,” Ann N Y Acad Sci 922:1–10.
122. 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,

123. Ludwig-Müller J. (2015). “Plants and endophytes: equal partners in secondary metabolite production,” Biotechnol Lett. (7):1325-34. Epub 2015 Mar 20. PMID: 25792513.J.
124. 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.
125. 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.
126. Manayi A, Nabavi S M, Setzer W N, Jafari S. (2019). “Piperine as a potential anti-cancer agent: a review on preclinical studies,” Curr Med Chem 25(37):4918–4928.
127. 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. Epub PMID: 21555147.
128. 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.
129. Melendez-Gonzalez C, Muria-González M J, Anaya A L, Hernández-Bautista B E, Hernández-Ortega S, González M C. (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.
130. 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.
131. Merino 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.
132. Metwaly A M, Fronczek F R, Ma G, Kadry H A, El-Hela A A, Mohammad A-EI. (2014). “Antileukemic α-pyrone derivatives from the endophytic fungus *Alternaria phragmospora*,” Tetrahedron Lett; 55(24): 3478-81.
133. Mishra A, Gond S K, Kumar A, Sharma V K, Verma S K, Kharwar R N. (2011). “Sourcing the fungal endophytes: a benefcial transaction of biodiversity, bioactive natural products, plant protection and nanotechnology. Microorg Sustain Agric Biotechnol. 978-94-007-2214-9_26
134. Moudi M, Go R, Yien C Y. S, and Nazre M. (2013). “Vinca alkaloids,” Int. J. Prev. Med. 4, 1231–1235.
135. 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.
136. Nadeem M, Ram M, Alam P, Ahmad M M, 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. AJMR11.1596.
137. Nadeem M, Rikhari H C, Kumar A, Palni LMS, Nandi S K. (2002). “Taxol content in the bark of Himalayan Yew in relation to tree age and sex,” Phytochemistry 60(6):627–631.
138. 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.
139. Nitiss, J L. (2009). “Targeting DNA topoisomerase II in cancer chemotherapy,” Nat. Rev. Cancer 9, 338–350
140. Noble R L, Beer C T Cutts J H. (1958). “Role of chance observations in chemotherapy: *Vinca rosea,”* Ann N Y A.cad Sci.;76(3):882-94. PMID: 13627916.
141. Noble R L. (1990). “The discovery of the vinca alkaloids—chemotherapeutic agents against cancer,” Biochem. Cell Biol. 68, 1
142. Noble R. (2016). “Anti-cancer alkaloids of *Vinca rosea*,” Pharmacol. Orient. Plants 7, 61–78.
143. Noumeur 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.
144. Ochoa-Villarreal M, Howat S, Hong S, Jang M O, Jin Y W, Lee EK, Loake G J. (2016). “Plant cell culture strategies for the production of natural products,” BMB Rep.;49(3):149-58. PMID: 26698871; PMCID: PMC4915229.
145. Ortega H E, Graupner P R, Asai Y, Tendyke K, Qiu D, Shen Y Y, Rios N, Arnold A E, Coley P D, Kursar T A, Gerwick W H, 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. Epub. PMID: 23560689.
146. Ouyang D Y, Zeng L H, Pan H, Xu L H, Wang Y, Liu K P, He X H. (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. Epub 2013. PMID: 23939040.
147. Palem P P, Kuriakose G C, 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.
148. Pan Q, Shikano I, Hoover K, Liu T.-X, Felton G. (2019). “*Enterobacter ludwigii*, isolated from the gut microbiota of *Helicoverpa zea*, promotes tomato plant growth and yield without compromising anti-herbivore defenses.” Arthropod-Plant Interactions. 13.
149. 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.
150. 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. Epub 2009 Oct 6. PMID: 19880222.
151. Patel B, Das S, Prakash R, Yasir M. (2010). “Natural bioactive compound with anticancer potential,” Int J Adv Pharm Sci 1:32–41
152. Pateraki I, Andersen-Ranberg J, Jensen N B, Wubshet S G, Heskes A M, Forman V, Hallström B, Hamberger B, Motawia M S, Olsen C E, Staerk D, Hansen J, Møller B L, Hamberger B. (2017). “Total biosynthesis of the cyclic AMP booster forskolin from Coleus forskohlii,” Elife;6: e23001. PMID: 28290983; PMCID: PMC5388535.
153. Prashith-Kekuda T R. (2016). “Isolation, characterization and antimicrobial potential of endophytic actinomycetes,” Int J Curr Microbiol Appl Sci 5:100–116.
154. 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.
155. 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.
156. 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

157. Puri S C, 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 R K, Qazi G N. (2006). "The endophytic fungus *Trametes hirsuta* as a novel alternative source of podophyllotoxin and related aryl tetralin lignans," J Biotechnol.;122(4):494-510. Epub 2005 Dec 20. PMID: 16375985.
158. 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
159. 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
160. 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.
161. 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
162. 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.
163. 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.
164. 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.
165. Raveendran V V. (2015). "Camptothecin-discovery, clinical perspectives and biotechnology," Nat Prod Chem Res.; 3:175.
166. Remesh A. (2017). "Toxicities of anticancer drugs and its management," Int. J. Basic Clin. Pharmacol. 1, 2–12.
167. Retna A M, Ethalsa P. (2013). "A review of the taxonomy, ethnobotany, chemistry and pharmacology of *Catharanthus roseus* (Apocyanaceae)," IJERT 2(10):3899–3912
168. Rowinsky E K, Onetto N, Canetta R M, Arbuck S G. (1992). "Taxol-the 1st of the texanes, an important new class of anti-tumor agents" Semin Oncol.; 19: 646-62.
169. S C B J, Mathew J, Radhakrishnan E K. (2017). "Endophytic *Phomopsis sp*. colonization in *Oryza sativa* was found to result in plant growth promotion and piperine production," Physiol Plant;160(4):437-446. Epub 2017 Jun 5. PMID: 28224643.
170. Salam N, Khieu T N, Liu M J, Vu T T, Chu-Ky S, Quach N T, Phi Q T, Narsing Rao M P, Fontana A, Sarter S, Li W J. (2017). "Endophytic Actinobacteria Associated with *Dracaena cochinchinensis* Lour.: Isolation, Diversity, and Their Cytotoxic Activities," Biomed Res Int. 2017:1308563. Epub. PMID: 28484706; PMCID: PMC5397652.
171. Sebola T E, Uche-Okereafor N C, Mekuto L, Makatini M M, Green E, Mavumengwana V. (2020). "Antibacterial and Anticancer Activity and Untargeted Secondary Metabolite Profiling of Crude Bacterial Endophyte Extracts from *Crinum macowanii* Baker Leaves," Int J Microbiol. PMID: 33488726; PMCID: PMC7803143.
172. Seehafer K, Rominger F, Helmchen G, Langhans M, Robinson D G, Özata B, Brugger B, Strating J R, van Kuppeveld F J, Klein CD. (2013). "Synthesis and biological properties of novel brefeldin A analogues," J Med Chem.;56(14):5872-84. Epub 2013 Jul 8. PMID: 23805957.
173. Selim M H, Karm Eldin el-Z, Saad M M, Mostafa el-S E, Shetia Y H, Anise A A. (2015). "Purification, Characterization of L-Methioninase from Candida tropicalis, and Its Application as an Anticancer," Biotechnol Res Int. 2015;2015: 173140. Epub 2015 Nov 24. PMID: 26691554; PMCID: PMC4672112.
174. 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,
175. Shiono Y, Kikuchi M, Koseki T, Murayama T, Kwon E, Aburai N, Kimura K I. (2011). "Isopimarane diterpene glycosides, isolated from endophytic fungus *Paraconiothyrium sp*.," MY-42. Phytochemistry 72:1400–1405
176. Shweta S, Gurumurthy B R, Ravikanth G, Ramanan U S, Shivanna M B. (2013). "Endophytic fungi from *Miquelia dentata* Bedd., produce the anti-cancer alkaloid, camptothecine. Phytomedicine" 20(3-4):337-42. j. phymed.2012.11.015. Epub 2012 Dec 27. PMID: 23273751.
177. Shweta S, Zuehlke S, Ramesha B T, 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. j. phytochem.2009.09.030. Epub 2009 Oct 26. PMID: 19863979.
178. 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
179. Singh R, Kumar A, Kapil D. Pandey, Singh M. (2017). "PGPR Isolates from the Rhizosphere of Vegetable Crop Momordica charantia: Characterization and Application as Biofertilizer," International Journal of Current Microbiology Applied Science, 6, 1789-1802.
180. 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.
181. 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
182. 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.
183. Stierle A, Strobel G, Stierle D. (1993). "Taxol and taxane production by *Taxomyces andreanae*, an endophytic fungus of Pacific yew," Science; 260:214–216.
184. Stojanovic-Radic Z, Pejˇcic M, Dimitrijevic M, Aleksic 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]
185. Strobel G, Daisy B, Castillo U, Harper J. (2004). "Natural products from endophytic microorganisms," J Nat Prod 67(2):257– 268.
186. 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
187. Swamy M K, Akhtar M S, Sinniah U R. (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.
188. Taechowisan T, Chaisaeng S, Phutdhawong W. (2017). "Antibacterial, antioxidant and anticancer activities of biphenyls from Streptomyces sp.," BO-07: an endophyte in Boesenbergia rotunda (L.) Mansf A. Food and Agricultural Immunology. 28. 1-17.

189. 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]
190. Tan R X, Zhou W X. (2001). “Endophytes: a rich source of functional metabolites,” Nat Prod Rep 18:448–459
191. 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
192. 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. (2019). “Isopenicins A.C. Two types of antitumor meroterpenoids from the plant endophytic fungus *Penicillium sp*.,” sh18. Org. Lett. 21, 771–775.
193. Thirumara R, Prendergast G C, Gilman P B. (2007). “Cytotoxic chemotherapy in clinical treatment of cancer,” Cancer Immunotherapy (pp. 101–116). Elsevier
194. Trapp M A, Kai M, Mithofer A, Rodrigues-Filho E. (2015). “Antibiotic oxylipins from *Alternanthera brasiliana* and its endophytic bacteria,” Phytochemistry 110:72–82
195. Turbyville T J, Kithsiri Wijeratne E M, Liu MX, Burns A M, Seliga C J, Luevano LA, David C L, Faeth S H, 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 desert,” J Nat Prod 69:178–184
196. 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. Epub PMID: 33996375; PMCID: PMC8116431.
197. Ulukan H, and Swaan P W. (2002). “Camptothecins.” Drugs 62, 2039–2057.
198. 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.
199. Uzma F, Mohan C D, Hashem A, Konappa N M, Rangappa S, Kamath P V, Singh B P, Mudili V, Gupta V K, Siddaiah C N, Chowdappa S, Alqarawi AA, Abd Allah EF. (2018). “Endophytic Fungi-Alternative Sources of Cytotoxic Compounds: A Review,” Front Pharmacol.;9:309. PMID: 29755344; PMCID: PMC5932204.
200. 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.
201. Venugopalan A, Srivastava S. (2015). “Endophytes as in vitro production platforms of high value plant secondary metabolites,” Biotechnol Adv.;33:873–87.
202. 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.
203. Wall M E, Wani M C. (1996). “Camptothecin and taxol: from discovery to clinic,” J Ethnopharmacol. (1-3):239-53; discussion 253-4. PMID: 9213622.
204. 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
205. Wang M., Sun, Z H, Chen Y C, Liu H X, Li H H, Tan G H, Li SN, Guo X L, Zhang W M, (2016). “Cytotoxic cochlioquinone derivatives from the endophytic fungus *Bipolaris sorokiniana* derived from *Pogostemon cablin*.” Fitoterapia 110, 77–82.
206. Wang Q X, Li S F, Zhao F, Dai H Q, Bao L, Ding R, Gao H, Zhang L X, Wen H A, Liu H W. (2011). “Chemical constituents from endophytic fungus *Fusarium oxysporum*.” Fitoterapia. Jul;82(5):777-81. Epub. PMID: 21497643.
207. 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.
208. 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.
209. Wang Y, Dai C C. (2011). “Endophytes: a potential resource for biosynthesis, biotransformation, and biodegradation” Ann Microbiol 61:207–215
210. 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
211. Wani M C, Horwitz S B. (2014). “Nature as a remarkable chemist: a personal story of the discovery and development of Taxol. Anticancer Drugs,” 25(5):482-7. PMID: 24413390; PMCID: PMC3980006.
212. Wani M C, Taylor H L, Wall M E, Coggon P, Mcphail A T. (1971). “Plant antitumor agents.VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*,” J Am Chem Soc 93(9):2325–2327.
213. Wheeler N C, Jech K, Masters S, Brobst S W, Alvarado A B, Hoover A J, Snader K M. (1992). “Effects of genetic, epigenetic, and environmental factors on taxol content in *Taxus brevifolia* and related species,” J Nat Prod.;55(4):432-40. PMID: 1355111.
214. Wijeratne E M, Bashyal B P, Liu M X, Rocha D D, Gunaherath G M, U'Ren J M, Gunatilaka M K, Arnold A E, Whitesell L, Gunatilaka A A. (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. Epub. PMID: 22264149; PMCID: PMC3359839.
215. 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,” Plant Genet Resour. 3 (2):90–100. 575 90 - 100.
216. Woodrow C J, Haynes R K, Krishna S. (2005). “Artemisinins,” Postgrad Med J. Feb;81(952):71-8. PMID: 15701735; PMCID: PMC1743191.
217. Wrasidlo W, Gaedicke G, Guy R K, Renaud J, Pitsinos E, Nicolaou K C, Reisfeld R A, Lode H N. (2002). “A novel 2'- (N-methylpyridinium acetate) prodrug of paclitaxel induces superior antitumor responses in preclinical cancer models,” Bioconjug Chem.;13(5):1093-9. PMID: 12236791.
218. Wu L S, Hu C L, Han T, Zheng C J, Ma X Q, Rahman K, Qin L P. (2013). “Cytotoxic metabolites from *Perenniporia tephropora*, an endophytic fungus from *Taxus chinensis* var. mairei.” Appl Microbiol Biotechnol.;97(1):305-15.
219. Wu Y Y, Lu C H, Qian X M, Huang Y J, Shen Y M. (2009). “Diversities within genotypes, bioactivity and biosynthetic genes of endophytic actinomycetes isolated from three pharmaceutical plants,” Curr Microbiol; 59:475-482.
220. Wu Z C, Li D L, Chen Y C, Zhang W M. (2010). “A new isofuranonaphthalenone and Benzopyrans from the endophytic fungus Nodulisporium sp.,” A4 from Aquilaria sinensis. Helv Chim Acta 93:920–924
221. 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
222. 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.
223. 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

224. Yamada Y, Kuzuyama T, Komatsu M, Shin-Ya K, Omura S, Cane D E, Ikeda H. (2015). "Terpene synthases are widely distributed in bacteria," Proc Natl Acad Sci U S A.;112(3):857-62. Epub 2014 Dec 22. PMID: 25535391; PMCID: PMC4311827.
225. Yang X-L, Li Z-Z. (2013). "New spiral γ-lactone enantiomers from the plant endophytic fungus *Pestalotiopsis foedan*. Molecules," 2013; 18(2): 2236-42.
226. Yang Y, Zhao H, Barrero RA, Zhang B, Sun G, Wilson I W, Xie F, Walker K D, Parks J W, 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. PMID: 24460898; PMCID: PMC3925984.
227. Ying Y M, Shan W G, Zhang L W, Zhan ZJ. (2013). "Ceriponols A–K, tremulane sesquitepenes from Ceriporia lacerate HS-ZJUTC13A, a fungal endophyte of *Huperzia serrata*," Phytochemistry 95:360–367
228. 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
229. Yuan Z, Tian Y, He F, Zhou H. (2019). "Endophytes from *Ginkgo biloba* and their secondary metabolites. Chin Med 14:51.
230. 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.
231. Zaiyou J, Li M, Xiqiao H. (2017). "An endophytic fungus efficiently producing paclitaxel isolated from *Taxus wallichiana* var. mairei," Medicine.;96: e7406.
232. 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
233. Zhan J, Burns A M, Liu M X, Faeth S H, Gunatilaka A A L. (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.
234. 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.
235. 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]
236. 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.
237. 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."
238. 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.
239. Zheng J, Zhou Y, Li Y, Xu DP, Li S, Bin Li H. (2016). "Spices for prevention and treatment of cancers," Nutrients 8:495.
240. Zhou J Y, Yuan J, Li X, Ning Y F, Dai C C. (2015). "Endophytic bacterium triggered reactive oxygen species directly increase oxygenous sesquiterpenoid content and diversity in *Atractylodes lancea*," Appl Environ Microbiol 82:1577–1585
241. 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