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

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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 gives an opportunity to learn about novel compounds via exclusive beneficial properties for malignancies treatments. While comparing chemically and natural medications, natural medications have considerable therapeutic effectiveness and are reasonable. A plant's healthy intracellular or intercellular environment is habitat to a certain type of microorganism they are termed as endophytes. Endophytic fungi inhabiting medicinal plants exhibit an eclectic spectrum of chemical entities and also, they govern the host plant's synthesis of certain secondary metabolites. These endophytic fungi can serve as an exciting source of multiple chemicals having cancer-fighting qualities. 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 collaboration that occur between endophytes and plants host that enables the synthesis of novel secondary metabolites. Insight from such a review would provide a rapidly developing area of inquiry in the creation of unique secondary metabolites by fungal endophytes. 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 remains as the most prevalent trigger of death by cancer. There exist hundreds of distinct types of cancer that diverge with regard to their behaviour and therapy response. 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. Natural medicinal products synthesis from plants never reaches the necessary level, and it is evolved under precise environmental conditions, stress at a specific developmental stage or during nutrient availability. The biggest difficulties posed by using 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 endophytic substances that are active can include other products besides those produced by hosts plants (Wang and Dai 2011). Endophytes colonise plant tissues despite generating any disease symptoms (Bacon and White 2016). The secondary metabolites isolated from endophytes show an array of different kinds 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 microbial entities 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, basically 16% or less than of the described fungal species have undergone profound cultivation and exploration. Globally, there are between 2.2 and 3.8 million different species of fungi (Hawksworth and Lucking 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 forms of cancer that consequence in the demand for other natural phytochemicals of therapeutic value (Remesh, 2017). An extensive range of biologically active substances comprise steroids, alkaloids, terpenoids, quinones, flavonoids, and a few others with distinctive structures and a number of pharmaceutical characteristics 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 rationale 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.

II. ENDOPHYTIC ACTINOMYCETES

Actinomycetes of various genera associated with diverse parts of plants are termed endophytic actinomycetes. They form one of the most relevant supplies of novel phytochemicals having many pharmaceutical as well as agricultural values. A diverse array of bioactivities such as antiviral, anti-cancer, antimicrobial and antioxidant properties 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). A00066 and A00089 *Amycolatopsis* sp., are actinomycetes secluded 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 detrimental to cell lines of cancer or tumor cells 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 broadly distributed environmental microorganisms that bring about bioactive substances that are effective towards phytopathogens (Xue et al., 2013; Zeng et al., 2013). Streptomyces is the largest genus among the actinomycetes and they belong to the Streptomycetaceae family (Kampfer 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 actions contrary to Gram-positive bacteria and antioxidant and strong anticancer actions (Taechowisan et al., 2017)

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

The favorable 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 an enormous amount of production of desired metabolites (Bertrand et al., 2014). While the bacterium *Bacillus subtilis* 168 trpC2 and endophytic fungi *Aspergillus versicolor* KU258497 are co-cultured, two distinct variants of 3,4-dihydronaphthalen-(2 H)-1-one (1-tetralone) are developed. 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 composites with their host. For instance, 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 on account of 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 exhibit anthracyclines production and antimicrobial actions and also portrayed cytotoxic and antifungal actions contray to 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 thru mixed foliar sprays with irrigation (Gao et al., 2015). For instance, some L-asparaginase and neoplastic cells functioning catalyses the conversion of L-asparagine. L-Asparaginase was added to multi-drug treatment with acute lymphoblastic leukemia in both children and adults, 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* leaf tissue can biosynthesize substances with bioactive properties and be bioprospecting for therapeutic use into

antibacterial and cancer fighting 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). Cell reduction about 43% at 100 μg/mL against A549 lung carcinoma cells was shown by *Raoultella ornithinolytica* endophyte, crude extract. Anti-cancer activity opposed to 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 drop of 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 claim that endophytes can break down the host plant's secondary metabolites, 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 goods made from endophytic fungus 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 cell damaging action contrary to one of the analysed cell lines, and 39% of the extracts exhibited >50% inhibited progress against all of the examined 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 supply 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*, that is secluded from the plant *Capsicum annum* (Clark and Lee 2016; Devari et al., 2014). 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 potential anticancer herbs, including *Podophyllum peltatum* and *Juniperus recurve* (Ardalani et al., 2017). Three mellenin derivatives secluded from the *Penicillium sp.* from Senecio favus 5-methylmellein, 6-hydroxymellein, and 4-hydroxymellein 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 robust anticancer catalyst 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 plenty of investigations dealing with the fungal diversities in plants having medicinal values (Dhayanithy et al., 2019; Biswas et al., 2020; Wang et al., 2016)

Secondary metabolites synthesized by fungal 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 *Taxus brevifolia*, a Pacific yew tree (Stierle et al., 1993). The CHCl3 extract of *Pantoea agglomerans* from, for instance, demonstrated strong action against the hepatic carcinoma- cell line HepG2 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* several additional taxus species, ranging from *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 first billion-dollar anticancer medication ever developed, 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 employed in the production process of paclitaxel (Zaiyou et al., 2017). When a culture fermentation is augmented with certain advantageous elements like antecedents, carbon sources, metabolite bypass blockers, inducers, and supplies of nitrogen 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 upsurge in taxol production was obtained by using the method of induced production, in a prior analysis, it was established that the administration of benzoic acid to a fungus called *Periconia* sp. that was linked to *Torreya grandifolia* promoted the production of taxol. 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). Autonomous immense level generation 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 lung cancer cell that is not very small (NSCLC), ovarian cancer, breast cancer, *kaposi sarcoma* correlated with AIDS, and AIDS-related Kaposi sarcoma can all be treated with paclitaxel alone or in conjunction with other anticancer therapies. This was sanctioned by the (FDA) Food and Drug Administration (Krown et al., 2020). Among 4 different endophytic fungi secluded out of the bark of *Taxus baccata, Stemphylium* sp. fungal strain was the one involved in the production of Taxol (Zaiyou et al., 2017). During the early 1990's the structure of paclitaxel was officially launched on 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). The process for the production of Taxol carried out using a number of species from endophytic genera., 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 focusing on the mitochondrial system, proteins blocking programmed cell death for instance immune cells, and (Bcl-2) B-cell Leukemia 2 (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 impressions of tumour necrosis factor-related (programmed cell death) 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 (making use of paclitaxel-specific monoclonal antibodies), thin layer chromatography, spectroscopy (Matrix-assisted laser desorption/ionization—Time of flight [MALDI-TOF]), high-performance liquid chromatography as well as [NMR] nuclear magnetic resonance, are used to find paclitaxel in endophytes extracts (Flores Bustamante et al., 2010).

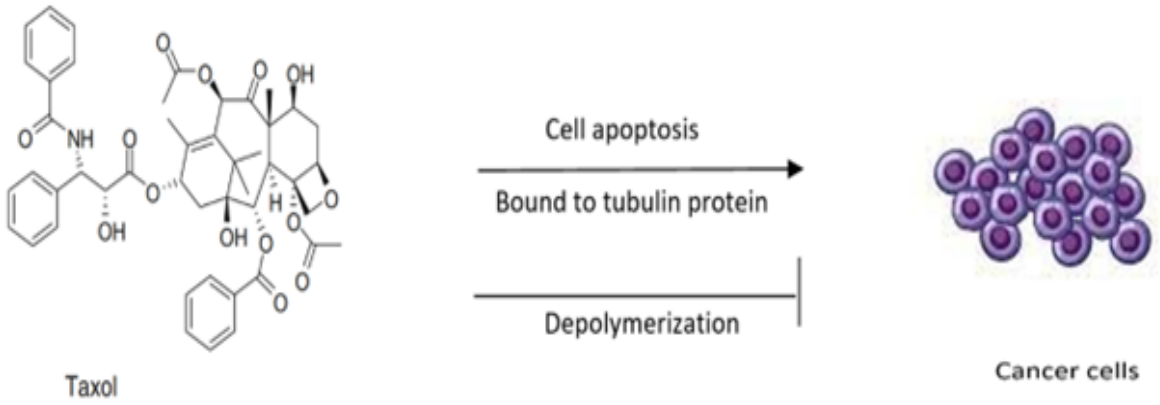


Figure: 1

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) as well as (VP-16-213) etoposide 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 semi-synthetic variants like Etoposide, Etopophos and Teniposide were served 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 in order generate plant-origin natural compounds (Ochoa-Villarreal et al., 2016). *WB5121 Fusarium* Strain Linked to *Dysosma Versipellis* was reported to produce a maximal output of 277 g/g of dry-weight mycelia during the seclusion of podophyllotoxin (Tan et al., 2017). Fungal endophytes such as *T. hirsute*, *Phialocephala fortinii* and *J. communis* L. Horstmann, 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 evolved complexes has been extensively used. Podophyllotoxin is produced by the fungus *Fusarium solani*, which is endophytic and has its origin in the root *Podophyllum hexandrum* plant 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 podophyllotoxin about 29.0 µg/g in support of this reports revealed *Fusarium solani* another strain releasing podophyllotoxin about 29.0 µg/g (Nadeem et al., 2012). *Alternaria tenuissima*, an endophyte that produces podophyllotoxin, appears to be affiliated with *Sinopodophyllum emodi* L. root (Liang et al., 2016). The knowledge of the process through which endophytic fungi develop 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). (FACS) Fluorescence-activated cell sorting 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 carbamate derivative includes (A549) human lung adenocarcinoma cells, HeLa cells, (HCT-8) human colon carcinoma cells and (HL-60) human promyelocytic leukaemia cells sensitivity to a derivative of carbamate known as 4 β -(1,2,3-triazol-1-yl) podophyllotoxin (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 collaboration along with the topoisomerase II enzyme (Cortés and Pastor, 2003). At the Xinglong Mountains, Gansu Province, China fungal endophyte Alternaria *tenuissima* was secluded 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 ideally capable to generate podophyllotoxin-related substance like, podophyllotoxin glucoside and dimethoxy podophyllotoxin. *Trametes hirsuta* partnered alongside *Podophyllum hexandrum*'s rhizome 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).

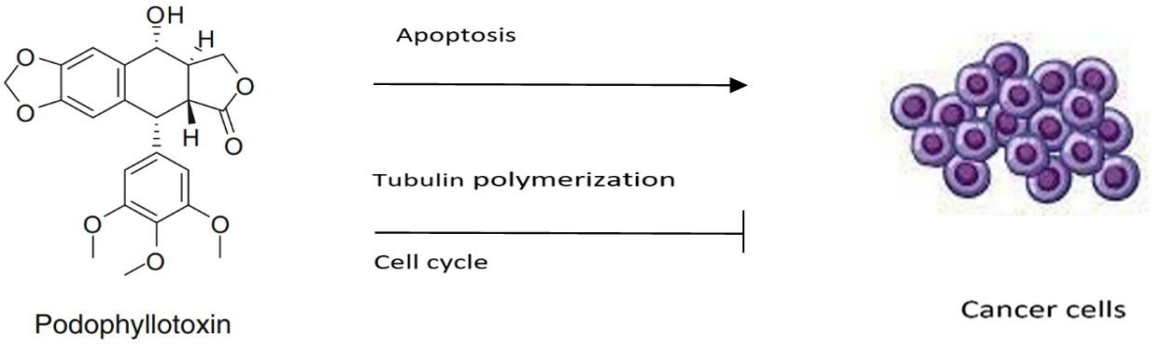


Figure: 2

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 complex DNA covalent's, commonly referred to as topoisomerase II toxins 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 an outcome of the things, the death of epithelial cells is caused by the cell cycle detention 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 because of the mismatch between microtubule assembly and

breakdown created as a result of podophyllotoxin, and tubulin binding (Guerram et al., 2012). In cancer cells, it starts a stress signalling cascade in the (ER) endoplasmic reticulum that foster 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 out of the root system of podophyllum species, *Podophyllum peltatum* L. and (Berberidaceae) *Podophyllum emodi* Wallich (Stahelin, 1973)

C. Camptothecin

Camptothecin (CPT) 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 in the making 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 incorporating mathematical patterns [artificial neural networks (ANN) along with response surface methodology (RSM)], bioreactor optimizations, biochemical engineering methods, etc., were employed. In recent years, RS effectively optimized a few or more response factors in pharmacologically important 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 (PDA/ PDB) Potato dextrose medium is a promising media for cultivation of fungal strains from CPT-producing plants (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 an indole moiety as well as a seco-iridoid into alkaloids, those 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 enzyme topoisomerase 1 cleavage complex interacts with camptothecin and its derivatives, stabilizing the catalysts as a consequence 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, it culminates in the cleavable complex along with an intermediate covalent response. They primarily eliminate cells in the S-phase by collisions that might be deadly between moving replication forks and cleavable topo-I complexes, and the cytotoxicity of CPT was brought on by collisions with the transcription machinery that led to the creation of long-lived to (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 output 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 via FDA to support the therapy of ovarian cancer, small-cell lung cancer, along with colorectal cancer about 40 years after the discovery of *C. acuminata* extract's anticancer efficacy (Blagosklonny 2004).

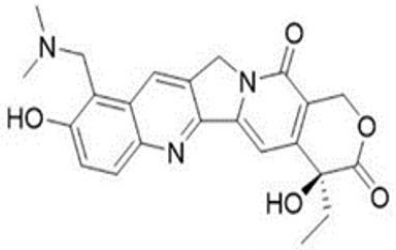


Figure 3: Topotecan

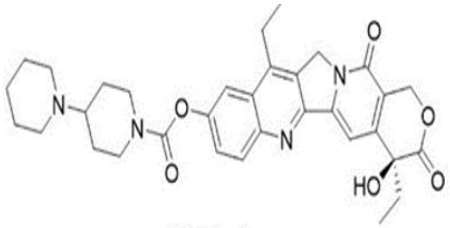


Figure 4: Irinotecan

Other than *Camptotheca acuminata* another seven families produce Camptothecin they are Piperaceae (*Piper betel*), Rubiaceae (*Ophiorrhiza alata, Ixora coccinea*), Gelsemiaceae (Mostueabrunonis), Violaceae (*Rinorea anguifera*), 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. In endophyte *Trichoderma atroviride* with camptothecin, there was a yield amplification (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* secluded out of *Nothapodytes foetida*'s tissues from inner bark produce camptothecin with an absorption of dry weight mycelia at a rate of 18 g/mg and demonstrated cell detrimental actions against (A549) human carcinoma cells, OVCAR-5 ovarian cancer cell as well as HEp2 from the liver cancer cell (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 deemed to be effective cancer prevention tools for example IDEC-132 (9-amino camptothecin), rubitecan (9-nitro camptothecin) as well as 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* family Rubiaceae, (Nyssaceae) *Camptotheca acuminata*, and (Icacinaceae) *Nothapodytes nimmoniana*, include candidate genes for CPT synthesis and critical enzymes for its control (Manjunatha et al., 2016; Rather et al., 2017).

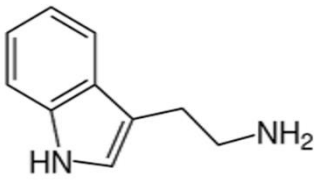


Figure 5: Tryptamine

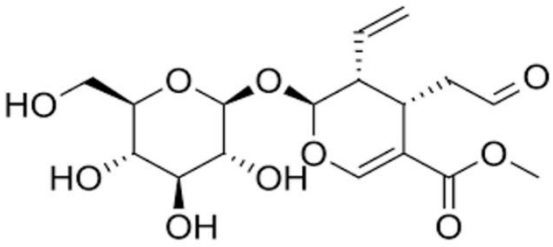


Figure 6: Secologanin

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 fungus *Fusarium solani*, which is an endophyte displayed maximal detrimental impact on a cancerous cell (Ran et al., 2017). Using high-performance liquid chromatography, it was detected that *Aspergillus niger* also produces camptothecin and it was separated by way from the *Piper betel*. Additionally, impact of cell detrimental activity was found within cell lines of colon cancer (Aswini and Soundhari 2018). When all of the important variables in a fungus cultivation were optimized, the best CPT production bring about 146 mg/l including an array of fungal cultures (FI + F2) was discovered. Experimentally, these results were contrasted with those obtained from *Colletotrichum fructicola* F1(33 mg/l) monoculture along with (69 mg/l) *Corynespora cassiicola*-F2 monoculture colonies. *Nothapodytes nimmoniana* monocultures of *Fusarium oxysporum* secluded out of the same plant supplied high amounts of CPT (90 mg/l) on their own (Bhalkar et al., 2016). Endophytic fungi in *Camptotheca acuminata* that were observed in the bark of plant found to produce camptothecin were detected again (Kusari et al., 2009). Three fungi that produce camptothecin have been isolated from *C. acuminata*: LY341, LY355 *Aspergillus sp*. along with *Trichoderma atroviride* LY357; their respective earnings were 7.93, 42.92, 197.82 g/L. With repetitive subculture nevertheless, strains LY341 and LY355 were incapable to generate camptothecin. But from the second to eighth generation unswerving camptothecin production was observed in LY357 strain (Kai et al., 2015). 3 varieties of fungi *Phomopsis vaccinii* (XSCY02), (XSXY09) *Fusarium nematophilum* and (XSQZ04) *Alternaria alternate* 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 campothecin 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 *Fusarium solani* (S-019) is the sole fungus that among 94 strains located out of *Camptotheca acuminata*, 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).

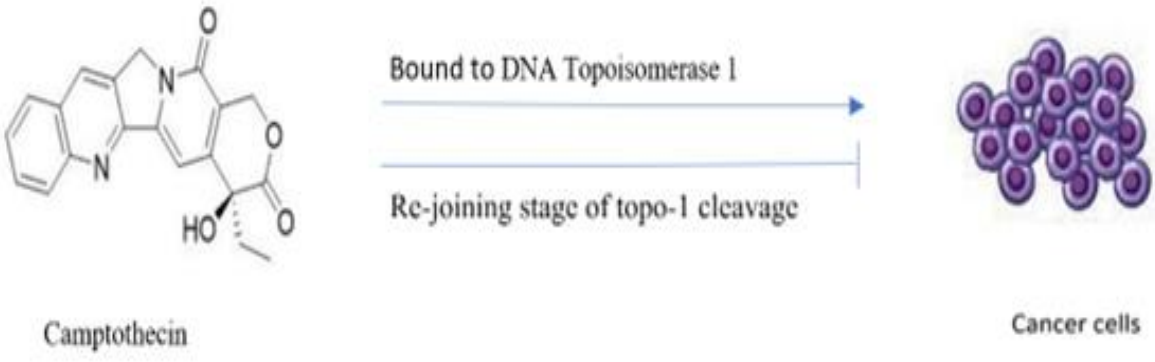


Figure: 7

D. Vinca alkaloids

Leaves of vinca plants are the natural supplies of bioactive compounds. Vinca plant leaves had been put to use for centuries to cure a variety of illnesses. Academics have stated that it also has hypoglycaemic, 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 compounds, vinblastine and vincristine are the natural vinca alkaloids that are derived from *Vinca rosea* or *Catharanthus roseus* and are used to treat lymphoma and leukaemia correspondingly (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 hypoglycaemic 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 fixing it. The way that cells interact with vinca alkaloids generates the 1a (p21) CDK (cyclin dependent kinase) as well as tumor-associated protein p53, which affect the protein kinase action. 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 secluded 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 employed 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). In the fight against different malignancies, vinca alkaloids are the second-highest often used class of drugs for cancer treatment. The coupling of catharanthine monomer and vindoline resulted in the formation of terpenoid indoles vinca alkaloids, and owing to their capacity to lower the quantity of white blood cells in nephroblastoma and severe lymphoblastic leukaemia, they are utilized in chemotherapy (Moudi et al., 2013). Over the course of a decade, the extract was thoroughly studied phytochemically, and plenty of cancer-fighting alkaloids were identified, particularly vinblastine, vincristine, vinleunosine, and vinrosidine (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 very 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. Regarding phase-II/III trials for medical therapy of malignancies and breast cancer, vinca alkaloids along with structural analogues (such as vinflunine, vinorelbine, and anhydro vinblastine) 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 as well as vinblastine secluded 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 out 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 developmental restraint in the HeLa, MCF7, A549, U251 and A431 cell lines. Though, significant impacts were not observed on normal cells HEK293 (Palem et al., 2016; Song et al., 2016).

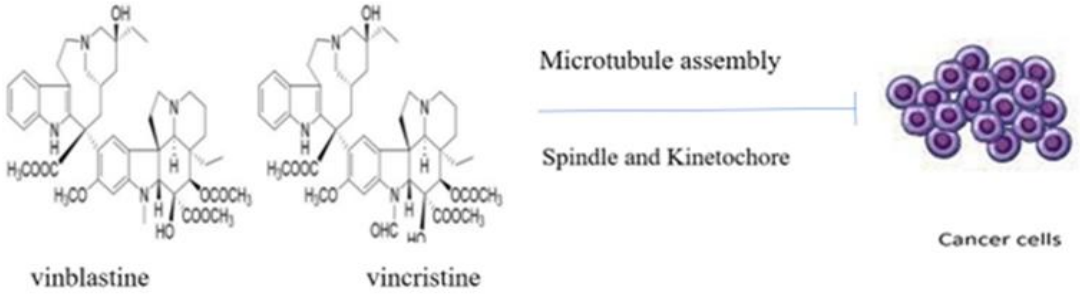


Figure: 8

E. Piperine

The fruits of certain kinds of plants contain piperine, that include pepper plants such as *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, an upsurge in apoptotic signalling pathway, control of mitotic catastrophe, and reduction in 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 hinders 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: stimulation 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-κB transcription factors, restriction of ERK1/2, an enzyme that is controlled by extracellular signals, AKT signalling pathways as well p38 MAPK and inhibits matrix metalloproteinase (MMP)-9 expression signal matrix metalloproteinase (MMP)-9 expression stimulated by (EGF) epidermal growth factor-induced (Stojanovi et al., 2019).

The anti-cancer and anti-intrusive properties of piperine could be explained by suppressing MMP-13 as well MMP-9 production, which also reduce NF-κB and AP-1 activation and PKC and ERK phosphorylation, respectively (Hwang et al., 2011). According to recent research, piperine suppresses blood vessel formation 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 efficacy in boosting bioavailability of specific medications and minerals. The cultures of endophytic fungal species such as *Mycosphaerella* sp. C. *gloeosporioides*, and *Periconia* sp. secluded 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 supplier for seclusion of piperine (Chithra et al., 2017). Piperine restricts prostate carcinoma cells (LNCaP and PC3) via inducing death of cell, in addition to lowering mTORC1 activity in Caco-2 and HT-29 cells (Yun et al., 2013). In TRIAL (tumour necrosis factor-related apoptosis-prompting ligand) based therapy piperine is utilized as an adjuvant that inhibits the phosphorylation of survivin and p65 triggers caspase-mediated cell death in TRAIL-sensitive as well as TRAIL-resistant triple-negative breast carcinoma (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 demonstrate a variety of biological activity, most importantly they show anti-cancer properties (Grover et al., 2022). Two novel pyrans from *Alternaria phragmospora* endophytic fungi secluded from *Vinca rosea* leaves are 5-butyl-6-(hydroxymethyl)-4- methoxy-2H-pyran-2-one as well as 4-methoxy-6-methyl-5- (3- oxobutyl) -2H-pyran-2-one, those exhibited modest antileukemic activity contrary to HL60 cells (IC50 values of 2.2, 0.9 μM) and K562 cells (IC50 values of 4.5, 1.5 μM) (Metwaly et al., 2014). Fungal endophyte *Nodulisporium* sp. is secluded from the shoot part of *Aquilaria sinensis* discloses a novel benzopyran occurrence. 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 an enormous variety of biologically active metabolites. Through in vitro scrutiny of cytotoxic inhibition over 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 (Chen et al., 2016). Genus Aspergillus of fungal endophyte serves as the primary source of pyrone metabolites and its variants (Liu et al., 2011). Nigerapyrone B is the derivative of α-Pyrone discovered in the innermost 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. 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 (Huang et al., 2011).

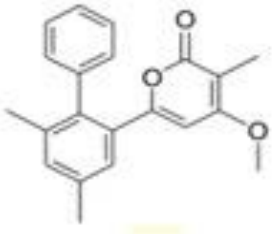
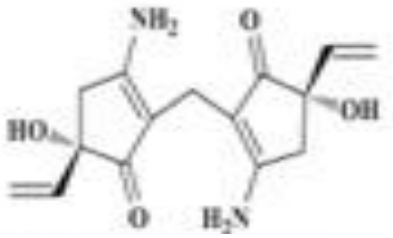
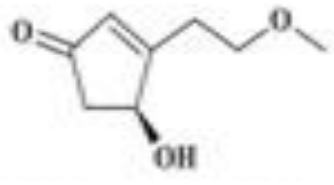


Figure 9: Nigerapyrones B

G. Alkaloids

Low molecular weight nitrogen-containing substances that are commonly referred to as alkaloids., 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 in alkaloids generated by flora have an extensive spectrum of biological actions, including toxicity, therapeutic benefits, and recreational uses. Studies have been conducted on various alkaloids generated from plants that have a vast array of bioactivities, including toxicity, therapeutic benefits, and recreational uses, several of them secluded from fungal endophytes. Alkaloids are obtained from plants for their conceivable utility as cancer-fighting medicines, lots of them are sourced from fungus 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, griffithiiene, an intriguing terpenoid-alkaloid skeleton-based chemical with significant efficacy towards pancreatic, bladder, alongside colon cancer cell lines, was generated by the endophytic fungus *Hypomontagnella monticulos* Zg15SU sourced from *Zingiber grifthii* (HCT116, Panc-1 and NBT-T2,) (Lutfa et al., 2021). Ascomylactams A–C are three new alkaloids mined from the mangrove plant fungal endophyte *Didymella* sp. of. 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 separated from *Hippeastrum calyptratum* Herb. and *Hippeastrum aulicum* Herb (Andrade et al., 2014). The biological properties of alkaloids generated from plants have a wide spectrum 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). 3 novel composites Atrichodermones A, B, and C isolated from endophytic *Trichoderma atroviride*, has anti-inflammatory effects counter to IL-1 β and TNF-α and cytotoxic action against U967 and HL60 cell lines (Zhou et al., 2017).





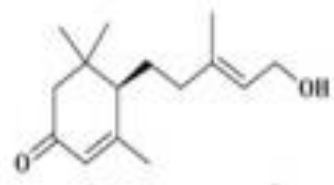


Figure 10: Atrichodermone A **Figure 11: Atrichodermone B** **Figure 12: Atrichodermone C**

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

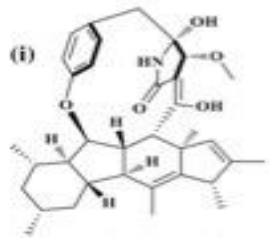


Figure 13: Ascomylactam

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, C as well chaetoviridin E were applied to the particular 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 termed as *Eurotium rubrum* that was secluded out of the t *Hibiscus tiliaceus* plant tissues (Wang et al., 2007). From the *Desmotes incomparabilis* leaf tissues isolated an endophytic fungus under *Mycoleptodiscus* sp. produces Mycoleptodiscus B, which has cancer-preventing action on 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 brought about by endophytic fungus *Pestalotiopsis photiniae* secluded from the plant *Roystonea Regia.* China. It possesses a MDA-MB-231 repressing effect (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 as well as (−) -(1R,4R,6S,7S)- 2-caren-4,8-olide, are two new terpenoids obtained from the *Periconia* sp. endophytic fungi isolated from the herb *Annona muricata.* These two substances exhibit negligible cytotoxic action in in-vitro tests counter to six human tumour cell lines (A2780, Bel-7402, HCT-8, BGC-823, MCF7, and A549) (Ge et al., 2011). Relatively all these extensively occurring metabolites are present in prokaryotes in a minor fraction (Yamada et al., 2015). Increased oxygenous sesquiterpenoid content of plant *A. lancea* (a therapeutic herb in China, comprising sesquiterpenoids with oxygen) 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 as well as cancer suppressing 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, Phomoarcherin B displayed in vitro cytotoxic effects over KKU-M139, KKU-100, KKU-M156, KKUM214, KKU-M213, and KB cell lines. Phomoarcherin C exhibited in vitro cytotoxic properties towards the KKU-M139, KKU-100, KKU-M156, KKU-M214 and KKU-M213 cell lines. IC50 values of 16.6, Phomoarcherin A demonstrated in vitro cytotoxic activity against KKU-M213 cell lines (Hemtasin et al., 2011). Fungal endophyte MY-42 of *Paraconiothyrium* sp. involved 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 conventional insecticides and anthelmintics found in the fruits as well as bark of *Melia azedarach* and *Melia toosendan* (TSN) plants (Wang et al., 2007). TSN acts as a potential antitumor drug against various tumours and involves estrogen receptor (ER) and p53 protein upregulation, stimulation of the mitochondrial programmed cell death 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 contrary to 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 developed out of a fungal endophyte *Cercospora* sp. secluded from the leaves of *Fallopia japonica*. Fungus *Cercosporene* F exhibits detrimental 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 correspondingly (Feng et al., 2014)

Forskolin is an active labdane diterpene substance. sequestered from the roots of *Coleus forskohlii*, Indian Coleus 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 cellular damage towards 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 secluded from the mangrove plant *Hibiscus tiliaceous* internal tissues produces a compound called 9-dehydroxyeurotinone has an anticancer action averse to SW1990 cell lines (Chen et al., 2016). 2,3-didehydro-19α-hydroxy14-epicochlioquinone B, the novel cytotoxic compound isolated from the species *Nigrospora*, MA75 residing in the shoot system 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 correspondingly (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 tyrosine derived dopaquinone, as well catechol oxidase, PKS creates catechol derived benzoquinone (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 retrieved through the culture of *Stemphylium globuliferum* an endophyte connected to the *Mentha pulegium* medicinal herb has an EC50 value of 2.7 g/mL and is harmful to the L5178Y cells that are malignant (Debbab et al., 2010).

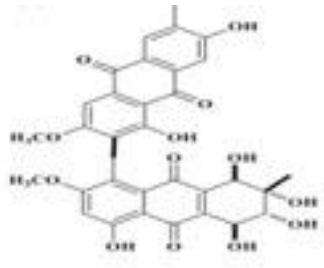


Figure 14: Alterporriol

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 as well MCF-7 (with IC50 values about 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	*T.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, MCF-7, PC-3 MDA-MB-435,	*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 piqued the scientific collective's curiosity, 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 possess a widespread devastating cytotoxic impact, depending over the tumour cell lines and 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.

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